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(12) (19) (CA) **Demande-Application**

(21) (A1) **2,328,720**
(86) 1999/04/19
(87) 1999/10/28

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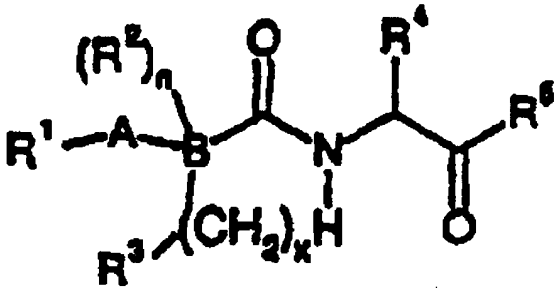
(51) Int.Cl.[6] C07D 295/12, C07D 213/70, C07D 317/58, A61K 31/50, C07C 237/32, C07D 213/30, C07D 215/24, C07C 311/21, C07C 311/08, C07D 215/06, C07D 207/06, C07D 403/04, C07D 217/04
(30) 1998/04/20 (198 17 460.8) DE

(54) **NOUVEAUX AMIDES HETEROCYCLIQUEMENT SUBSTITUES A ACTION DE PROTEASES DE CYSTEINE**

(54) **NOVEL HETEROCYCLICALLY SUBSTITUTED AMIDES WITH CYSTEINE PROTEASE-INHIBITING EFFECT**



(I)

(57) L'invention concerne des amides de la formule générale (I), qui sont des inhibiteurs d'enzymes, notamment de protéases de cystéine.

(57) The invention relates to amides of the general formula (I), which are inhibitors of enzymes, especially cysteine proteases.

PCT WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales Büro

INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation 6 :
C07D 295/12, A61K 31/50, C07D 403/04, 317/58, 207/06, 215/06, 215/24, 217/04, 213/70, 213/30, C07C 237/32, 311/08, 311/21

A1

(11) Internationale Veröffentlichungsnummer: **WO 99/54320**

(43) Internationales Veröffentlichungsdatum: 28. Oktober 1999 (28.10.99)

(21) Internationales Aktenzeichen: PCT/EP99/02620

(22) Internationales Anmeldedatum: 19. April 1999 (19.04.99)

(30) Prioritätsdaten:
198 17 460.8 20. April 1998 (20.04.98) DE

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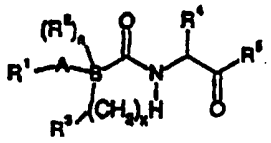
(81) Bestimmungsstaaten: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HR, HU, ID, IL, IN, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, ZA, eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Veröffentlicht
Mit internationalem Recherchenbericht.
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist; Veröffentlichung wird wiederholt falls Änderungen eintreffen.

48969
020602

(54) Title: NOVEL HETEROCYCLICALLY SUBSTITUTED AMIDES WITH CYSTEINE PROTEASE–INHIBITING EFFECT

(54) Bezeichnung: NEUE HETEROCYCLISCH SUBSTITUIERTE AMIDE MIT CYSTEIN–PROTEASE HEMMENDER WIRKUNG



(I)

(57) Abstract

The invention relates to amides of the general formula (I), which are inhibitors of enzymes, especially cysteine proteases.

(57) Zusammenfassung

Die Erfindung betrifft Amide der allgemeinen Formel (I), die Inhibitoren von Enzymen, insbesondere Cystein–Proteasen darstellen.

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NOVEL HETEROCYCLICALLY SUBSTITUTED AMIDES WITH CYSTEINE PROTEASE-INHIBITING EFFECT

The present invention relates to novel amides which are inhibitors of enzymes, especially cysteine proteases such as calpain (= calcium dependant cysteine proteases) and its isoenzymes and cathepsins, for example B and L.

Calpains are intracellular proteolytic enzymes from the group of cysteine proteases and are found in many cells. Calpains are activated by an increase in the calcium concentration, a distinction being made between calpain I or μ-calpain, which is activated by μ-molar concentrations of calcium ions, and calpain II or m-calpain, which is activated by m-molar concentrations of calcium ions (P. Johnson, Int. J. Biochem. 1990, 22(8), 811-22). Further calpain isoenzymes have now been postulated too (K. Suzuki et al., Biol. Chem. Hoppe-Seyler, 1995, 376(9), 523-9).

It is suspected that calpains play an important part in various physiological processes. These include cleavages of regulatory proteins such as protein kinase C, cytoskeletal proteins such as MAP 2 and spectrin, muscle proteins, protein degradation in rheumatoid arthritis, proteins in the activation of platelets, neuropeptide metabolism, proteins in mitosis and others which are listed in M.J. Barrett et al., Life Sci. 1991, 48, 1659-69 and K.K. Wang et al., Trends in Pharmacol. Sci., 1994, 15, 412-9.

Elevated calpain levels have been measured in various pathophysiological processes, for example: ischemia of the heart (e.g. myocardial infarct), of the kidney or of the central nervous system (e.g. stroke), inflammations, muscular dystrophies, cataracts of the eyes, injuries to the central nervous system (e.g. trauma), Alzheimer's disease etc. (see K.K. Wang,

above). It is suspected that there is a connection between these disorders and elevated and persistent intracellular calcium levels. This results in overactivation of calcium-dependent processes, which are then no longer subject to physiological control. Accordingly, overactivation of calpains may also induce pathophysiological processes.

It has therefore been postulated that inhibitors of calpain enzymes may be useful for treating these disorders. Various investigations have confirmed this. Thus, Seung-Chyul Hong et al., Stroke 1994, 25(3), 663-9 and R.T. Bartus et al., Neurological Res. 1995, 17, 249-58 have shown a neuroprotective effect of calpain inhibitors in acute neurodegenerative disorders or ischemias like those occurring after a stroke. Likewise, calpain inhibitors improved the recovery of the memory deficits and neuromotor disturbances occurring after experimental brain trauma (K.E. Saatman et al. Proc. Natl. Acad. Sci. USA, 1996, 93, 3428-3433). C.L. Edelstein et al., Proc. Natl. Acad. Sci. USA, 1995, 92, 7662-6, found a protective effect of calpain inhibitors on kidneys damaged by hypoxia. Yoshida, Ken Ischi et al., Jap. Circ. J. 1995, 59(1), 40-8, were able to show beneficial effects of calpain inhibitors after cardiac damage produced by ischemia or reperfusion. Since the release of the β-AP4 protein is inhibited by calpain inhibitors, a potential therapeutic use for Alzheimer's disease has been proposed (J. Higaki et al., Neuron, 1995, 14, 651-59). The release of interleukin-1α is likewise inhibited by calpain inhibitors (N. Watanabe et al., Cytokine 1994, 6(6), 597-601). It has further been found that calpain inhibitors have cytotoxic effects on tumor cells (E. Shiba et al. 20th Meeting Int. Ass. Breast Cancer Res., Sendai Jp, 1994, 25-28 Sept., Int. J. Oncol. 5 (Suppl.), 1994, 381).

Further possible uses of calpain inhibitors are detailed in K.K. Wang, Trends in Pharmacol. Sci., 1994, 15, 412-8.

Calpain inhibitors have already been described in the literature. However, these are predominantly either irreversible or peptide inhibitors. Irreversible inhibitors are usually alkylating substances and have the disadvantage that they react nonselectively or are unstable in the body. Thus, these inhibitors often show unwanted side effects such as toxicity, and are accordingly of limited use or unusable. The irreversible inhibitors can be said to include, for example, the epoxides E 64 (E.B. McGowan et al., Biochem. Biophys. Res. Commun. 1989, 158, 432-5), α-halo ketones (H. Angliker et al., J. Med. Chem. 1992, 35, 216-20) or disulfides (R. Matsueda et al., Chem. Lett. 1990, 191-194).

Many known reversible inhibitors of cysteine proteases such as calpain are peptide aldehydes, in particular dipeptide and tripepide [sic] aldehydes such as, for example, Z-Val-Phe-H (MDL 28170) (S. Mehdi, Tends [sic] in Biol. Sci. 1991, 16, 150-3). Under physiological conditions, peptide aldehydes have the disadvantage that, owing to the high reactivity, they are often unstable, may be rapidly metabolized and are prone to nonspecific reactions which may cause toxic effects (J.A. Fehrentz and B. Castro, Synthesis 1983, 676-78. JP 08183771 (CA 1996, 605307) and EP 520336 have described aldehydes derived from 4-piperidinoylamides [sic] and 1-carbonylpiperidino-4-ylamides [sic] as calpain inhibitors. However, the aldehydes which are claimed herein and are derived from amides of the general structure I with heteroaromatic substituents have not previously been described.

Peptide ketone derivatives are likewise inhibitors of cysteine proteases, in particular calpains. Thus, for

example, ketone derivatives where the keto group is activated by an electron-attracting group such as CF_3 are known to be inhibitors of serine proteases. In the case of cysteine proteases, derivatives with ketones activated by CF_3 or similar groups have little or no activity (M.R. Angelastro et al., J. Med. Chem. 1990, 33, 11-13). Surprisingly, to date only ketone derivatives in which, on the one hand, leaving groups in the α position cause irreversible inhibition and, on the other hand, the keto group is activated by a carboxylic acid derivative have been found to be effective inhibitors of calpain (see M.R. Angelastro et al., see above; WO 92/11850; WO 92,12140; WO 94/00095 and WO 95/00535). However, only peptide derivatives of these keto amides and keto esters have been described as effective (Zhaozhao Li et al., J. Med. Chem. 1993, 36, 3472-80; S.L. Harbenson et al., J. Med. Chem. 1994, 37, 2918-29 and see above M.R. Angelastro et al.).

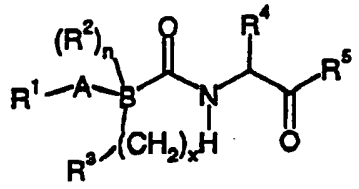
Ketobenzamides have already been described in the literature. Thus, the keto ester PhCO-Abu-$COOCH_2CH_3$ has been described in WO 91/09801, WO 94/00095 and 92/11850. The analogous phenyl derivative Ph-CONH-$CH(CH_2Ph)$-CO-$COCOOCH_3$ was, however, found to be only a weak calpain inhibitor in M.R. Angelastro et al., J. Med. Chem. 1990, 33, 11-13. This derivative is also described in J.P. Burkhardt, Tetrahedron Lett., 1988, 3433-36. The significance of the substituted benzamides has, however, never been investigated to date.

In a number of therapies, such as [lacuna] stroke, the active ingredients are administered intravenously, for example as infusion solution. To do this it is necessary to have available substances, in this case calpain inhibitors, which have adequate solubility in water so that an infusion solution can be prepared. Many of the described calpain inhibitors have, however, the disadvantage that they have only low or no

solubility in water and thus are unsuitable for intravenous administration. Active ingredients of this type can be administered only with ancillary substances intended to confer solubility in water (cf. R.T. Bartus et al. J. Cereb. Blood Flow Metab. 1994, 14, 537-544). These ancillary substances, for example polyethylene glycol, often have side effects, however, or are even incompatible. A non-peptide calpain inhibitor which is soluble in water without ancillary substances would thus be a great advantage. No such inhibitor has been described to date, and it would thus be novel.

Substituted non-peptide aldehydes, keto carboxylic esters and keto amide derivatives were described in the present invention. These compounds are novel and surprisingly show the possibility of obtaining potent non-peptide inhibitors of cysteine proteases, such as, for example, calpain, by incorporating rigid structural fragments. In addition, all the present compounds of the general formula I have at least one aliphatic amine radical and are thus able to bind [sic] salts with acids. A large number of these substances are soluble in water in a 0.5% strength solution at pH 0.4-5 and thus the show the required profile for intravenous administration as is necessary, for example, for stroke therapy.

The present invention relates to amides of the general formula I



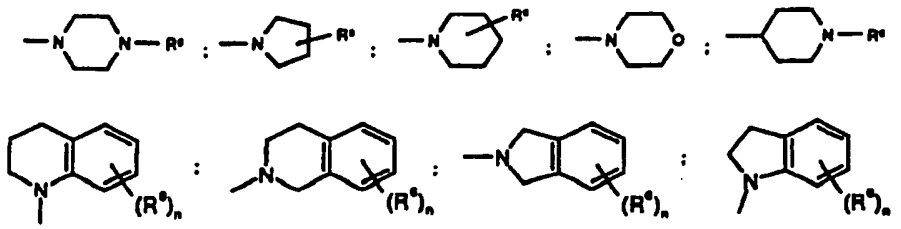
and their tautomeric and isomeric forms, possible enantiomeric and diastereomeric forms, and possible physiologically tolerated salts, in which the variables

have the following meanings:

R^1 can be hydrogen, C_1-C_6-alkyl, branched and unbranched, phenyl, naphthyl, quinolyl, pyridyl, pyrimidyl, pyrazyl, pyridazyl, quinazolyl, quinoxalyl, thienyl, benzothienyl, benzofuranyl, furanyl and indolyl, it being possible for the rings also to be substituted by up to 3 R^6 radicals, and

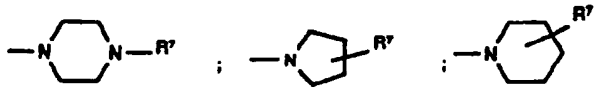
R^2 are hydrogen, C_1-C_6-alkyl, branched or unbranched, O-C_1-C_6-alkyl, branched or unbranched, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkyl-phenyl, C_2-C_6-alkenyl-phenyl, C_2-C_6-alkynyl-phenyl, OH, Cl, F, Br, I, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-alkyl, NHCO-C_1-C_4-alkyl, NHCO-phenyl, $CONHR^9$, $NHSO_2$-C_1-C_4-alkyl, $NHSO_2$-phenyl, SO_2-C_1-C_4-alkyl and SO_2-phenyl, and

R^3 can be NR^7R^8 or a ring such as



R^4 is -C_1-C_6-alkyl, branched or unbranched, which may also carry a phenyl, pyridyl or naphthyl ring which is in turn substituted by a maximum of two R^6 radicals, and

R^5 is hydrogen, $COOR^{11}$ and CO-Z in which Z is $NR^{12}R^{13}$ and



and

R^6 is hydrogen, C_1-C_4-alkyl, branched or unbranched, -O-C_1-C_4-alkyl, OH, Cl, F, Br, I, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-alkyl, -NHCO-C_1-C_4-alkyl, -NHCO-phenyl, -$NHSO_2$-C_1-C_4-alkyl, -$NHSO_2$-phenyl, -SO_2-C_1-C_4-alkyl and -SO_2-phenyl, and

R^7 is hydrogen, C_1-C_6-alkyl, linear or branched, and which may be substituted by a phenyl ring which itself may also be substituted by one or two R^{10} radicals, and

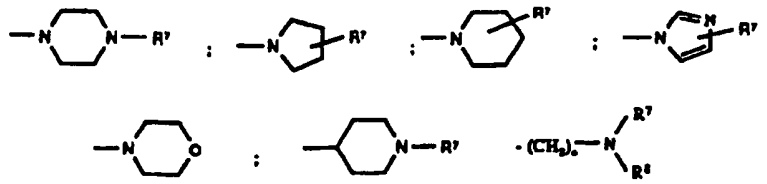
R^8 is hydrogen, C_1-C_6-alkyl, linear or branched, which may be substituted by a phenyl ring which may itself also be substituted by one or two R^{10} radicals, and

R^9 is hydrogen, C_1-C_6-alkyl, branched or unbranched, which may also carry a substituent R^{16}, or phenyl, pyridyl, pyrimidyl, pyridazyl, pyrazinyl, pyrazyl, naphthyl, quinolyl, imidazolyl, which may also carry one or two substituents R^{14}, and

R^{10} can be hydrogen, C_1-C_4-alkyl, branched or unbranched, -O-C_1-C_4-alkyl, OH, Cl, F, Br, I, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-alkyl, -NHCO-C_1-C_4-alkyl, -NHCO-phenyl, -$NHSO_2$-C_1-C_4-alkyl, -$NHSO_2$-phenyl, -SO_2-C_1-C_4-alkyl and -SO_2-phenyl

R^{11} is hydrogen, C_1-C_6-alkyl, linear or branched, and which may be substituted by a phenyl ring which may itself also be substituted by one or two R^{10} radicals, and

R^{12} is hydrogen, C_1-C_6-alkyl, branched and unbranched, and



[sic]

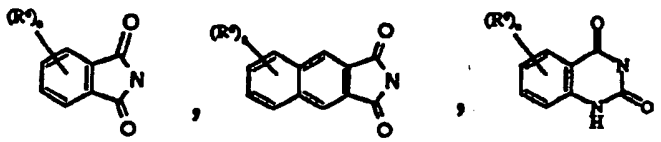
R^{13} is hydrogen, C_1-C_6-alkyl, branched or unbranched, which may also be substituted by a phenyl ring which may also carry an R^{10} radical, and by [lacuna]
and

R^{14} is hydrogen, C_1-C_6-alkyl, branched or unbranched, O-C_1-C_6-alkyl, branched or unbranched, OH, Cl, F, Br, I, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-alkyl, or two R^{14} radicals may represent a bridge $OC(R^{15})_2O$, and

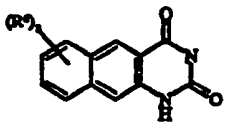
R^{15} is hydrogen, C_1-C_6-alkyl, branched and unbranched, and

R^{16} can be a phenyl, pyridyl, pyrimidyl, pyridazyl, pyrazinyl, pyrazyl, pyrrolyl, naphthyl, quinolyl, imidazolyl ring, which may also carry one or two substituents R^6, and

A is $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_o-$, $-(CH_2)_o-S-(CH_2)_m-$, $-(CH_2)_o-SO-(CH_2)_m-$, $-(CH_2)_o-SO_2-(CH_2)_m-$, $-CH=CH-$, $-C\equiv C-$, $-CO-CH=CH-$, $-(CH_2)_o-CO-(CH_2)_m-$, $-(CH_2)_m-NHCO-(CH_2)_o-$, $-(CH_2)_m-CONH-(CH_2)_o-$, $-(CH_2)_m-NHSO_2-(CH_2)_o-$, $-NH-CO-CH=CH-$, $-(CH_2)_m-SO_2NH-(CH_2)_o-$, $-CH=CH-CONH-$ and



and



[sic]

R^1-A together are also
[lacuna]
and

B is phenyl, pyridine, pyrimidine, pyrazine, imidazole and thiazole and

x is 1, 2 or 3, and

n is a number 0, 1 or 2, and

m, o is, independently of one another, a number 0, 1, 2, 3 or 4.

The compounds of the formula I can be employed as racemates, as enantiomerically pure compounds or as diastereomers. If enantiomerically pure compounds are required, these can be obtained, for example, by carrying out a classical racemate resolution with the compounds of the formula I or their intermediates using a suitable optically active base or acid. On the other hand, the enantiomeric compounds can likewise be prepared by using commercially purchasable compounds, for example optically active amino acids such as phenylalanine, tryptophan and tyrosine.

The invention also relates to compounds which are mesomers or tautomers of compounds of the formula I, for example those in which the aldehyde or keto group in formula I is in the form of an enol tautomer.

The invention further relates to the physiologically tolerated salts of the compounds I which can be obtained by reacting compounds I with a suitable acid

or base. Suitable acids and bases are listed, for example, in Fortschritte der Arzneimittelforschung, 1966, Birkhäuser Verlag, Vol. 10, pp. 224-285. These include, for example, hydrochloric acid, citric acid, tartaric acid, lactic acid, phosphoric acid, methanesulfonic acid, acetic acid, formic acid, maleic acid, fumaric acid etc., and sodium hydroxide, lithium hydroxide, potassium hydroxide and tris.

The amides I according to the invention can be prepared in various ways which has [sic] been outlined in the synthesis scheme.

Synthesis scheme

Heterocyclic carboxylic acids II are linked to suitable amino alcohols III to give the corresponding amides IV. Conventional peptide coupling methods are used for this, as detailed either in C.R. [sic] Larock, Comprehensive Organic Transformations, VCH Publisher, 1989, page 972 et seq., or in Houben-Weyl, Methoden der organischen Chemie, 4th edition, E5, Chapter V. It is preferred to use "activated" acid derivatives of II, with the acid group COOH being converted into a group COL. L is a leaving group such as, for example, Cl, imidazole and N-hydroxybenzotriazole. This activated acid is then reacted with amines to give the amides IV. The reaction takes place in anhydrous inert solvents such as methylene chloride, tetrahydrofuran and dimethylformamide at temperatures from -20 to +25°C.

These alcohol derivatives IV can be oxidized to the aldehyde derivatives I according to the invention. Various conventional oxidation reactions can be used for this (see C.R. [sic] Larock, Comprehensive Organic Transformations, VCH Publisher, 1989, page 604 et seq.) such as, for example, Swern and Swern-analogous oxidations (T.T. Tidwell, Synthesis, 1990, 857-70), sodium hypochloride [sic]/TEMPO (S.L. Harbenson et al., see above) or Dess-Martin (J. Org. Chem. 1983, 48, 4155). Preferably used for this are inert aprotic

solvents such as dimethylformamide, tetrahydrofuran or methylene chloride with oxidizing agents such as DMSO/py x SO_3 or DMSO/oxalyl chloride at temperatures from -50 to +25°C, depending on the method (see above literature).

Alternatively, the carboxylic acid II can be reacted with amino hydroxamic acid derivatives VI to give benzamides VII. The reaction in this case is carried out in the same way as for preparing IV. The hydroxamic derivatives VI can be obtained from the protected amino acids V by reaction with a hydroxylamine. An amide preparation process already described is also used in this case. Elimination of the protective group X, for example Boc, takes place in a normal way, for example with trifluoroacetic acid. The amide hydroxamic acids VII obtained in this way can be converted by reduction into the aldehydes I according to the invention. The reducing agent used for this is, for example, lithium aluminum hydride at temperatures from -60 to 0°C in inert solvents such as tetrahydrofuran or ether.

Carboxylic acids or acid derivatives such as esters IX (P = COOR', COSR') can also be prepared in analogy to the last process and can likewise be converted by reduction into the aldehydes I according to the invention. These processes are listed in R.C. Larock, Comprehensive Organic Transformations, VCH Publisher, 1989, pages 619-26.

The amides I according to the invention, which have heterocyclic substituents and have a keto amide or keto ester group, can be prepared in various ways which have been outlined in synthesis schemes 2 and 3.

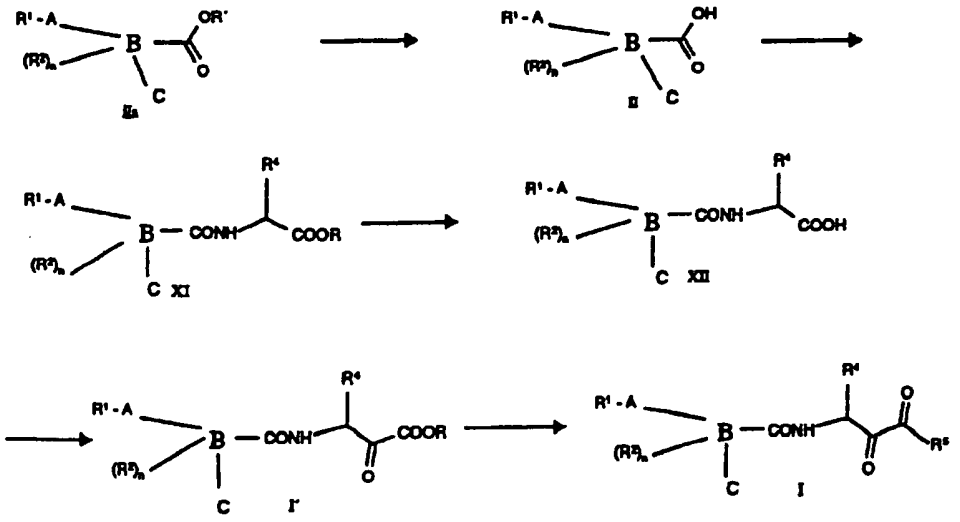
The carboxylic esters IIa are converted, where appropriate, with acids or bases such as lithium hydroxide, sodium hydroxide or potassium hydroxide in aqueous medium or in mixtures of water and organic

solvents such as alcohols or tetrahydrofuran at room temperature or elevated temperatures, such as 25-100°C, into the acids II.

These acids II are linked to an α-amino acid derivative using customary conditions which are listed, for example, in Houben-Weyl, Methoden der organischen Chemie, 4th edition, E5, Chapter V, and C.R. [sic] Larock, Comprehensive Organic Transformations, VCH Publisher, 1989, Ch. 9.

For example, the carboxylic acids II are converted into the "activated" acid derivatives IIb = Y-COL, where L is a leaving group such as Cl, imidazole and N-hydroxybenzotriazole, and then converted into the derivative XI by adding an amino acid derivative $H_2N-CH(R^3)-COOR$. This reaction takes place in anhydrous inert solvents such as methylene chloride, tetrahydrofuran and dimethylformamide at temperatures from -20 to +25°C.

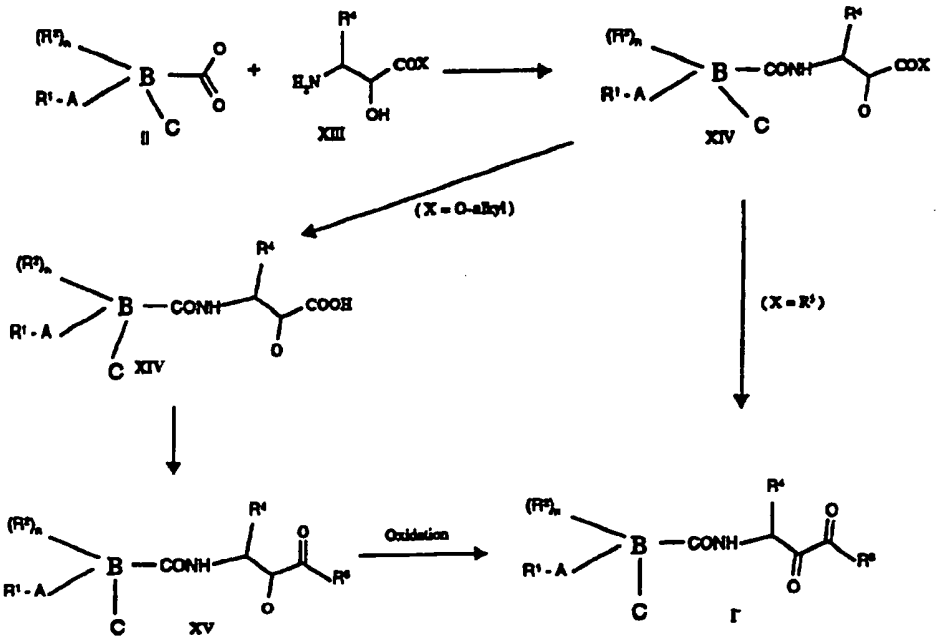
Scheme 1



The derivatives XI, which are usually esters, are converted into the keto carboxylic acids XII by hydrolysis analogous to that described above. The keto esters I' are prepared in a Dakin-West-analogous reaction using a method of ZhaoZhao Li et al., J. Med. Chem., 1993, 36, 3472-80. This entails a [sic] carboxylic acids such as XII being reacted with oxalic monoester chloride at elevated temperature (50-100°C) in solvents such as, for example, tetrahydrofuran, and the product obtained in this way then being reacted with bases such as sodium ethanolate in ethanol at temperatures of 25-80°C to give the keto ester I' according to the invention. The keto esters I' can be hydrolyzed as described above for example to keto carboxylic acids according to the invention.

The reaction to give keto benzamides I' likewise takes place in analogy to the method of ZhaoZhao Li et al. (see above). The keto group in I' is protected by adding 1,2-ethanedithiol with Lewis acid catalysis, such as, for example, boron trifluoride etherate, in inert solvents such as methylene chloride at room temperature, resulting in a dithiane. These derivatives are reacted with amines R^3-H in polar solvents such as alcohols at temperatures of 0-80°C, resulting in the keto amides I (R^4 = Z or NR^7R^8).

Scheme 2



An alternative method is depicted in scheme 2. The keto carboxylic acids II are reacted with amino hydroxy carboxylic acid derivatives XIII (for preparation of XIII, see S.L. Harbenson et al., J. Med. Chem. 1994, 37, 2918-29 or J.P. Burkhardt et al. Tetrahedron Lett. 1988, 29, 3433-3436) using customary peptide coupling methods (see above, Houben-Weyl), resulting in amides XIV. These alcohol derivatives XIV can be oxidized to the keto carboxylic acid derivatives I according to the invention. It is possible to use for this various customary oxidation reactions (see C.R. [sic] Larock, Comprehensive Organic Transformations, VCH Publisher, [lacuna] page 604 et seq.) such as, for example, Swern and Swern-analogous oxidations, preferably dimethyl sulfoxide/pyridine-sulfur trioxide complex in solvents such as methylene chloride or tetrahydrofuran, where appropriate with the addition of dimethyl sulfoxide, at room temperature or temperatures from -50 to 25°C (T.T. Tidwell, Synthesis 1990, 857-70) or sodium

hypochloride [sic]/TEMPO (S.L. Harbenson et al., see above).

In the case of α-hydroxy esters XIV (X = O-alkyl), these can be hydrolyzed to carboxylic acids XV using methods analogous to those above, but preferably using lithium hydroxide in water/tetrahydrofuran mixtures at room temperature. Other esters or amides XVI are prepared by reaction with alcohols or amines under coupling conditions described above. The alcohol derivative XVI can be oxidized to give keto carboxylic acid derivatives I according to the invention.

The preparation of the carboxylic esters II had already been described for some instances, or it takes place by usual chemical methods.

Compounds in which X is a bond are prepared by conventional aromatic coupling, for example Suzuki coupling with boric acid derivatives and halides with palladium catalysis or copper-catalyzed coupling of aromatic halides. The alkyl-bridged radicals (X = $-(CH_2)_m-$) can be prepared by reducing the analogous ketones or by alkylating the organolithium, e.g. ortho-phenyloxazolidines, or other organometallic compounds (cf. I.M. Dordor et al., J. Chem. Soc. Perkins Trans. I, 1984, 1247-52).

Ether-bridged derivatives are prepared by alkylating the corresponding alcohols or phenols with halides.

The sulfoxides and sulfones can be obtained by oxidizing the corresponding thioethers.

Alkene- and alkyne-bridged compounds are prepared, for example, by the Heck reaction from aromatic halides and corresponding alkenes and alkynes (cf. I. Sakamoto et al., Chem. Pharm. Bull., 1986, 34, 2754-59).

The chalcones are produced by condensing acetophenones with aldehydes and can, where appropriate, be converted into the analogous alkyl derivatives by hydrogenation.

Amides and sulfonamides are prepared from the amines and acid derivatives in analogy to the methods described above.

The dialkylaminoalkyl substituents are obtained by reductive amination of the aldehyde derivatives with the appropriate amines in the presence of boron hydrides such as the BH_3/pyridine complex or or [sic] $NaBH_3CN$ (A.F. Abdel-Magid, C.A. Maryanoff, K.G. Carson, Tetrahedron Lett. 10990 [sic], 31, 5595; A.E. Moormann, Synth. Commun. 1993, 23, 789).

The amides I with heterocyclic substituents of the present invention are inhibitors of cysteine proteases, especially cysteine proteases such as calpains I and II and cathepsins B and L.

The inhibitory effect of the amides I with heterocyclic substituents has been determined using enzyme assays known from the literature, determining as criterion of effect a concentration of the inhibitor at which 50% of the enzyme activity is inhibited (= IC_{50}). The amides I were measured in this way for their inhibitory effect on calpain I, calpain II and cathepsin B.

Cathepsin B assay

The inhibition of cathepsin B was determined by a method analogous to that of S. Hasnain et al., J. Biol. Chem., 1993, 268, 235-40.

2 µl of an inhibitor solution prepared from inhibitor and DMSO (final concentrations: 100 µM to 0.01 µM) are added to 88 µl of cathepsin B (cathepsin B from human liver (Calbiochem), diluted to 5 units in 500 µM

buffer). This mixture is preincubated at room temperature (25°C) for 60 minutes and then the reaction is started by adding 10 µl of 10 mM Z-Arg-Arg-pNA (in buffer with 10% DMSO). The reaction is followed in a microtiter plate reader at 405 nM [sic] for 30 minutes. The IC_{50}s are then determined from the maximum gradients.

Calpain I and II assay

The testing of the inhibitory properties of calpain inhibitors takes place in buffer with 50 mM tris-HCl, pH 7.5; 0.1 M NaCl; 1 mM dithiotreithol [sic]; 0.11 mM $CaCl_2$, using the fluorogenic calpain substrate Suc-Leu-Tyr-AMC (25 mM dissolved in DMSO, Bachem/ Switzerland). Human µ-calpain is isolated from erythrocytes, and enzyme with a purity > 95%, assessed by SDS-PAGE, Western blot analysis and N-terminal sequencing, is obtained after several chromatographic steps (DEAE-Sepharose, phenyl-Sepharose, Superdex 200 and blue Sepharose). The fluorescence of the cleavage product 7-amino-4-methylcoumarin (AMC) is followed in a Spex Fluorolog fluorimeter at λex = 380 nm and λem = 460 nm. The cleavage of the substrate is linear in a measurement range of 60 min., and the autocatalytic activity of calpain is low, if the tests are carried out at temperatures of 12°C. The inhibitors and the calpain substrate are added to the test mixture as DMSO solutions, and the final concentration of DMSO ought not to exceed 2%.

In a test mixture, 10 µl of substrate (250 µM final) and then 10 µl of µ-calpain (2 µg/ml final, i.e. 18 nM) are added to a 1 ml cuvette containing buffer. The calpain-mediated cleavage of the substrate is measured for 15 - 20 min. Then 10 µl of inhibitor (50-100 µM solution in DMSO) are added and the inhibition of cleavage is measured for a further 40 min.

K_i values are determined using the classical equation for reversible inhibition:
(Methods in Enzymology,)

Ki = I(v0/vi)-1; where I = inhibitor concentration, v0 = initial rate before addition of the inhibitor; vi = reaction rate at equilibrium.

The rate is calculated from v = AMC liberation/time, i.e. height/time.

Calpain is an intracellular cysteine protease. Calpain inhibitors must pass through the cell membrane in order to prevent intracellular proteins from being broken down by calpain. Some known calpain inhibitors, such as, for example, E 64 and leupeptin, cross cell membranes only poorly and accordingly show only a poor effect on cells, although they are good calpain inhibitors. The aim is to find compounds better able to cross membranes. Human platelets are used to demonstrate the ability of calpain inhibitors to cross membranes.

Calpain-mediated breakdown of tyrosine kinase pp60src in platelets

Tyrosine kinase pp60src is cleaved by calpain after activation of platelets. This has been investigated in detail by Oda et al. in J. Biol. Chem., 1993, Vol. 268, 12603-12608. This revealed that the cleavage of pp60src can be prevented by calpeptin, a calpain inhibitor. The cellular efficacy of our substances was tested based on this publication. Fresh, citrated, human blood was centrifuged at 200 g for 15 min. The platelet-rich plasma was pooled and diluted 1:1 with platelet buffer (platelet buffer: 68 mM NaCl, 2.7 mM KCl, 0.5 mM $MgCl_2 \times 6\ H_2O$, 0.24 mM $NaH_2PO_4 \times H_2O$, 12 mM $NaHCO_3$, 5.6 mM glucose, 1 mM EDTA, pH 7.4). After a centrifugation step and washing step with platelet

buffer, the platelets were adjusted to 10^7 cells/ml. The human platelets were isolated at RT.

In the assay mixture, isolated platelets (2×10^6) were preincubated with various concentrations of inhibitors (dissolved in DMSO) at 37°C for 5 min. The platelets were then activated with 1 µM ionophore A23187 and 5 mM $CaCl_2$. After incubation for 5 min., the platelets were briefly centrifuged at 13,000 rpm, and the pellet was taken up SDS sample buffer (SDS sample buffer: 20 mM Tris-HCl, 5 mM EDTA, 5 mM EGTA, 1 mM DTT, 0.5 mM PMSF, 5 µg/ml leupeptin, 10 µg/ml pepstatin, 10% glycerol and 1% SDS). The proteins were fractionated in a 12% gel, and pp60src and its 52 kDa and 47 kDa cleavage products were identified by Western blotting. The polyclonal rabbit antibody used, anti-cys-src ($pp60^{c\text{-}src}$), was purchased from Biomol Feinchemikalien (Hamburg). This primary antibody was detected using a second, HRP-coupled goat antibody (Boehringer Mannheim, FRG). The Western blotting was carried out by known methods.

The cleavage of pp60src was quantified by densitometry, using as controls unactivated (control 1: no cleavage) and ionophore- and calcium-treated platelets (control 2: corresponds to 100% cleavage). The ED_{50} corresponds to the concentration of inhibitor at which the intensity of the color reaction is reduced by 50%.

Glutamate-induced cell death in cortical neurones

The test was carried out as in Choi D.W., Maulucci-Gedde M.A. and Kriegstein A.R., "Glutamate neurotoxicity in cortical cell culture". J. Neurosci. 1989, 7, 357-368.

The cortex halves were dissected out of 15-day old mouse embryos and the single cells were obtained enzymatically (trypsin). These cells (glia and cortical neurones) are seeded out in 24-well plates. After three

days (laminin-coated plates) or seven days (ornithine-coated plates), the mitosis treatment is carried out with FDU (5-fluoro-2-deoxyuridines [sic]). 15 days after preparation of the cells, cell death is induced by adding glutamate (15 minutes). After removal of glutamate, the calpain inhibitors are added. 24 hours later, the cell damage is estimated by determining lactate dehydrogenase (LDH) in the cell culture supernatant.

It is postulated that calpain is also involved in apoptotic cell death (M.K.T. Squier et al., J. Cell. Physiol. 1994, 159, 229-237; T. Patel et al. Faseb Journal 1996, 590, 587-597). For this reason, in another model, cell death was induced in a human cell line with calcium in the presence of a calcium ionophore. Calpain inhibitors must get inside the cell and inhibit calpain there in order to prevent the induced cell death.

Calcium-mediated cell death in NT2 cells

Cell death can be induced in the human cell line NT2 by calcium in the presence of the ionophore A 23187. 10^5 cells/well were plated out in microtiter plates 20 hours before the test. After this period, the cells were incubated with various concentrations of inhibitors in the presence of 2.5 µM ionophore and 5 mM calcium. 0.05 ml of XTT (Cell Proliferation Kit II, Boehringer Mannheim) was added to the reaction mixture after 5 hours. The optical density was determined approximately 17 hours later, in accordance with the manufacturer's information, in an SLT Easy Reader EAR 400. The optical density at which half the cells have died is calculated from the two controls with cells without inhibitors incubated in the absence and presence of ionophore.

Elevated glutamate activities occur in a number of neurological disorders of psychological disturbances and lead to states of overexcitation or toxic effects in the central nervous system (CNS). The effects of glutamate are mediated by various receptors. Two of these receptors are classified, in accordance with the specific agonists, as NMDA receptor and AMPA receptor. Antagonists to these glutamate-mediated effects can thus be employed for treating these disorders, in particular for therapeutic use for neurodegenerative disorders such as Huntington's chorea and Parkinson's disease, neurotoxic impairments after hypoxia, anoxia, ischemia and after lesions like those occurring after stroke and trauma, or else as antiepileptics (cf. Arzneim. Forschung 1990, 40, 511-514; TIPS, 1990, 11, 334-338; Drugs of the Future 1989, 14, 1059-1071). De [sic]

Protection from cerebral overexcitation by excitatory amino acids (NMDA and AMPA antagonism in mice)

Intracerebral administration of excitatory amino acids (EAA) induces such drastic overexcitation that it leads to convulsions and death of the animals (mice) within a short time. These signs can be inhibited by systemic, e.g. intraperitoneal, administration of centrally acting substances (EAA antagonists). Since excessive activation of EAA receptors in the central nervous system plays a significant part in the pathogenesis of various neurological disorders, it is possible to infer from the detected EAA antagonism in vivo that the substances may have therapeutic uses for such CNS disorders. As a measure of the efficacy of the substances, an ED_{50} was determined, at which 50% of the animals are free of signs, owing to the previous i.p. administration of the measured substance, by a fixed dose of either NMDA or AMPA.

The amides I with heterocyclic substituents are inhibitors of cysteine derivatives [sic] such as calpain I and II and cathepsin B and L, and can thus be used to control diseases associated with an elevated activity of calpain enzymes or cathepsin enzymes. The present amides I can accordingly be used to treat neurodegenerative disorders occurring after ischemia, trauma, subarachnoid hemorrhages and stroke, and neurodegenerative disorders such as multi-infarct dementia, Alzheimer's disease, Huntington's disease and epilepsies and, in addition, to treat damage to the heart after cardiac ischemia, damage to the kidneys after renal ischemia, skeletal muscle damage, muscular dystrophies, damage caused by proliferation of smooth muscle cells, coronary vasospasms, cerebral vasospasms, cataracts of the eyes, restenosis of the blood vessels after angioplasty. In addition, the amides I may be useful in the chemotherapy of tumors and metastasis thereof and for treating disorders in which an elevated interleukin-1 level occurs, such as inflammation and rheumatic disorders.

The pharmaceutical preparations according to the invention comprise a therapeutically effective amount of the compounds I in addition to conventional pharmaceutical ancillary substances.

The active ingredients can be present in the usual concentrations for local external use, for example in dusting powders, ointments or sprays. As a rule, the active ingredients are present in an amount of from 0.001 to 1% by weight, preferably 0.001 to 0.1% by weight.

For internal use, the preparations are administered in single doses. From 0.1 to 100 mg are given per kg of body weight in a single dose. The preparation may be administered in one or more doses each day, depending on the nature and severity of the disorders.

The pharmaceutical preparations according to the invention comprise, apart from the active ingredient, the customary excipients and diluents appropriate for the required mode of administration. For local external use it is possible to use pharmaceutical ancillary substances such as ethanol, isopropanol, ethoxylated castor oil, ethoxylated hydrogenated castor oil, polyacrylic acid, polyethylene glycol, polyethylene glyco [sic] stearate, ethoxylated fatty alcohols, liquid paraffin, petrolatum and wool fat. Suitable examples for internal use are lactose, propylene glycol, ethanol, starch, talc and polyvinylpyrrolidone.

It is also possible for antioxidants such as tocopherol and butylated hydroxyanisole, and butylated hydroxy-toluene, flavor-improving additives, stabilizers, emulsifiers and lubricants to be present.

The substances which are present in the preparation in addition to the active ingredient, and the substances used in producing the pharmaceutical preparations, are toxicologically acceptable and compatible with the active ingredient in each case. The pharmaceutical preparations are produced in a conventional way, for example by mixing the active ingredient with other [sic] customary excipients and diluents.

The pharmaceutical preparations can be administered in various ways, for example orally, parenterally, such as intravenously by infusion, subcutaneously, intra-peritoneally and topically. Thus, possible presentations are tablets, emulsions, solutions for infusion and injection, pastes, ointments, gels, creams, lotions, dusting powders and sprays.

Examples

Example 1

2-((4-Phenylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

a) Methyl 2-(4-phenyl-1-piperazinylmethyl)benzoate

10.0 g of methyl 2-chloromethylbenzoate, 15 g of potassium carbonate, 8.8 g of N-phenylpiperazine and a spatula-tip of 18-crown-6 in 200 ml of DMF were heated at 100°C for 5 h and then stirred at room temperature for 60 h. The excess potassium carbonate was filtered off, the filtrate was concentrated, and the residue was partitioned between water and ethyl acetate. Drying of the organic phase over magnesium sulfate and removal of the solvent resulted in 16.8 g (100%) of the product.

b) 2-(4-phenyl-1-piperazinylmethyl)benzoic acid

16.8 g of intermediate 1a were introduced into 150 ml of THF, and 1.7 g of LiOH in 150 ml of water were added at room temperature. The cloudy solution was clarified by adding 10 ml of MeOH. The reaction mixture was stirred at room temperature for 12 h and hydrolyzed with an equimolar amount of 1 M HCl. The reaction mixture was evaporated to dryness, and the residue was taken up in methanol/toluene. Removal of the solvent resulted in 15.2 g (86%) of the product, which still contained salt.

c) 2-((4-Phenylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-ol-2-yl)amide

3.0 g of intermediate 1b and 3 ml of triethylamine were introduced into 50 ml of DMF. 5 g of sodium sulfate were added and the mixture was stirred for 30 min. 1.5 g of phenylalaninol, 1.4 g of HOBT and 2.1 g of EDC were successively added at 0°C, and the mixture was stirred at room temperature overnight. The reaction mixture was poured into distilled water, made alkaline with $NaHCO_3$, saturated with NaCl and extracted three times with 100 ml of methylene chloride. The organic phases were washed twice with water and dried over magnesium sulfate. Removal of the solvent resulted in 2.5 g (59%) of the product.

d) 2-((4-Phenylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

2.3 g of intermediate 1c were introduced into 50 ml of DMSO in the presence of 2.4 g of triethylamine, and 2.5 g of SO_3/pyridine complex were added. The mixture was stirred at room temperature overnight. The mixture was poured into 250 ml of distilled water, made alkaline with $NaHCO_3$, saturated with NaCl and extracted with 100 ml of methylene chloride, and the organic phase was dried over magnesium sulfate. After removal of the solvent, the residue was dissolved in THF, and the hydrochloride was precipitated with HCl in dioxane. The precipitate was filtered off with suction and washed several times with ether, resulting in 1.9 g (71%) of the product.

^{1}H-NMR (d_6-DMSO): δ = 2.9 (2H), 3.0-3.3 (8H), 4.1-4.5 (2H), 4.7 (1H), 6.8-7.7 (14H), 9.3 (1H), 9.8 (1H) ppm.

Example 2

2-((4-Benzylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

a) Methyl 2-((4-benzyl-1-piperazinyl)methyl)benzoate [sic]

10.0 g of methyl 2-chlorobenzoate and 9.6 g of N-benzylpiperazine were reacted in 200 ml of DMF in the presence of 15 g of potassium carbonate at 100°C in analogy to Example 1a, resulting in 17.6 g (100%) of the product.

b) 2-((4-Benzyl-1-piperazinyl)methyl)benzoic [sic] acid

17.5 g of intermediate 2a in 150 ml of THF were hydrolyzed with 1.6 g of LiOH in 150 ml of water in analogy to Example 1b, resulting in 9.1 g (54%) of the product.

c) 2-((4-Benzylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-ol-2-yl)amide

3.0 g of intermediate 2b were reacted in 60 ml of DMF with 3 ml of triethylamine, 1.5 g of phenylalaninol, 1.3 g of HOBT and 2.0 g of EDC in analogy to Example 1c, resulting in 2.0 g (46%) of the product.

d) 2-((4-Benzylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

1.5 g of intermediate 2c were oxidized in 40 ml of DMSO with 1.9 g of SO_3/pyridine complex in 20 ml of DMSO in the presence of 2.3 ml of triethylamine in analogy to Example 1d, resulting in 0.4 g (21%) of the product in the form of the fumarate.

^{1}H-NMR (d_6-DMSO): δ = 2.1-2.3 (8H), 2.9-3.0 (1H), 3.3-3.6 (6H), 4.5 (1H), 6.6 (2H), 7.1-7.7 (14H), 9.7 (1H), 10.3 (1H) ppm.

Example 3

2-((4-Benzylpiperazin-1-yl)methyl)benzoic acid N-(1-carbamoyl-1-oxo-3-phenylpropan-2-yl)amide

a) 2-((4-Benzylpiperazin-1-yl)methyl)benzoic acid N-(1-carbamoyl-1-ol-3-phenylpropan-2-yl)amide

1.5 g of intermediate 2b were reacted in 40 ml of DMF with 0.7 ml of triethylamine, 1.0 g of 3-amino-2-hydroxy-4-phenylbutyramide hydrochloride, 0.6 g of HOBT and 0.9 g of EDC in analogy to Example 1c, resulting in 0.8 g (38%) of the product.

b) 2-((4-Benzylpiperazin-1-yl)methyl)benzoic acid N-(1-carbamoyl-1-oxo-3-phenylpropan-2-yl)amide

0.7 g of intermediate 3a were oxidized in 20 ml of DMSO with 0.7 g of SO_3/pyridine complex in the presence of 0.8 g of triethylamine in analogy to Example 1d, resulting in 0.1 g (18%) of the product in the form of the free base.

^{1}H-NMR (d_6-DMSO): δ = 2.3 (4H), 2.8-3.5 (8H), 5.3 (1H), 6.7-7.5 (16H), 7.8 (1H), 8.1 (1H), 10.3 (1H) ppm.

Example 4

2-(4-((3-Methylphenyl)piperazin-1-yl)methyl)benzoic acid N-(1-carbamoyl-1-oxo-3-phenylpropan-2-yl)amide

a) Methyl 2-(4-((3-methylphenyl)-1-piperazinyl)-methyl)benzoate [sic]

4.0 g of methyl 2-chloromethylbenzoate and 4.4 g of 3-methylphenylpiperazine were heated in 200 ml of DMF in the presence of 4.5 g of potassium carbonate at 140°C for 3 h. The reaction mixture was poured into water and extracted three times with ethyl acetate. The combined organic phases were washed three times with saturated brine, dried over magnesium sulfate and concentrated, resulting in 6.5 g (92%) of the product.

b) 2-(4-((3-Methylphenyl)-1-piperazinyl)methyl)-benzoic [sic] acid

5.9 g of intermediate 4a were dissolved in 75 ml of THF and hydrolyzed with 0.9 g of LiOH in 75 ml of water in analogy to Example 1b, resulting in 2.9 g (51%) of the product.

c) 2-(4-((3-Methylphenyl)piperazin-1-yl)methyl)-benzoic acid N-(1-carbamoyl-1-ol-3-phenylpropan-2-yl)amide

1.8 g of intermediate 4b were introduced into 50 ml of DMF in the presence of 2.7 ml of triethylamine, and 0.8 g of HOBT, 1.3 g of 3-amino-2-hydroxy-4-phenylbutyramide hydrochloride and 1.2 g of EDC were successively added, in analogy to Example 1c, resulting in 1.4 g (50%) of the product.

d) 2-(4-((3-Methylphenyl)piperazin-1-yl)methyl)-benzoic acid N-(1-carbamoyl-1-oxo-3-phenylpropan-2-yl)amide

1.2 g of intermediate 4c were dissolved in 30 ml of DMSO and oxidized with 1.6 g of SO_3/pyridine

complex in the presence of 1.5 ml of triethylamine in analogy to Example 1d, resulting in 1.0 g (83%) of the product.

MS: m/e = 484 (M^+)

Examples 5 and 6 were synthesized in analogy to Example 1.

Example 5

3-((4-Phenylpiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide fumarate

^{1}H-NMR (d_6-DMSO): δ = 2.5 (4H), 2.9 (1H), 3.2 (4H), 3.3 (1H), 3.7 (2H), 4.5 (1H), 6.6 (2H), 6.75 (1H), 6.9 (2H), 7.2 (2H), 7.2-7.3 (5H), 7.45 (1H), 7.55 (1H), 7.75 (1H), 7.8 (2H), 8.9 (1H), 9.7 (1H) ppm.

Example 6

3-((4-(2-tert-Butyl-4-trifluoromethylpyrimidin-6-yl)-homopiperazin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

MS: m/e = 568 (M^++1)

Example 7

4-(N-(3,4-Dioxomethylene)benzyl-N-methylaminomethyl)-benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

a) 4-(N-(3,4-Dioxomethylene)benzyl-N-methylaminomethyl)benzoic acid

11.5 g of N-(3,4-dioxomethylene)benzyl-N-methylamine and 15.5 g of triethylamine were introduced into [lacuna], and 15.0 g of 4-bromomethylbenzoic acid in 100 ml of THF were

added. The reaction mixture was briefly heated to reflux and then stirred at room temperature for 15 h. After filtering off the salts, the mother liquor was concentrated, and the residue was dissolved in ethyl acetate and washed with water. The aqueous phase was made alkaline and extracted several times with ethyl acetate, resulting in 6.6 g (32%) of the product as a white solid.

b) 4-(N-(3,4-Dioxomethylene)benzyl-N-methylaminomethyl)benzoic acid N-(3-phenylpropan-1-ol-2-yl)-amide

4.4 g of intermediate 5a [sic] were introduced into 50 ml of DMF in the presence of 2.9 g of triethylamine, and 1.8 g of HOBT, 2.0 g of phenylalaninol and 2.8 g of EDC were successively added, in analogy to Example 1c, resulting in 2.3 g (40%) of the product.

c) 4-(N-(3,4-Dioxomethylene)benzyl-N-methylaminomethyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)-amide

2.0 g of intermediate 5b [sic] were dissolved in 60 ml of DMSO and oxidized with 2.1 g of SO_3/pyridine complex in the presence of 1.8 ml of triethylamine in analogy to Example 1d, resulting in 1.3 g (68%) of the product.

^{1}H-NMR (CF_3COOD): δ = 2.9 (3H), 3.2 (2H), 4.3-4.9 (5H), 6.1 (2H), 6.6 (1H), 6.9 (3H), 7.2-7.4 (5H), 7.8 (2H), 8.25 (2H) ppm.

MS: m/e = 430 (M^+)

Examples 8-28 were prepared in analogy to Example 7.

Example 8

4-(N-Benzyl-N-methylaminomethyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

^{1}H-NMR (CF_3COOD): δ = 2.9 (3H), 3.2 (2H), 4.3-5.0 (5H), 6.7 (1H), 7.25-7.5 (8H), 7.55 (2H), 7.8 (2H), 8.2 (2H) ppm.

MS: m/e = 386 (M^+)

Example 9

4-(N-(4-Methoxy)benzyl-N-methylaminomethyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

^{1}H-NMR (CF_3COOD): δ = 2.9 (3H), 3.3 (2H), 4.0 (3H), 4.3-4.9 (5H), 6.7 (1H), 7.1-7.4 (7H), 7.5 (2H), 7.8 (2H), 8.2 (2H) ppm.

MS: m/e = 416 (M^+)

Example 10

4-(N-Benzyl-N-methylaminomethyl)benzoic acid N-(3-butan-1-al-2-yl)amide

^{1}H-NMR (CF_3COOD): δ = 1.1 (3H), 1.6 (2H), 2.0 (2H), 2.9 (3H), 4.3-4.5 (3H), 4.7 (1H), 4.8 (1H), 6.6 (1H), 7.3-7.6 (5H), 7.8 (2H), 8.3 (2H) ppm.

MS: m/e = 338 (M^+)

Example 11

4-(N-(3,4-Dioxomethylene)benzyl-N-methylaminomethyl)-benzoic acid N-(3-butan-1-al-2-yl)amide

^{1}H-NMR (CF_3COOD): δ = 1.1 (3H), 1.6 (2H), 1.9 (2H), 2.9 (3H), 4.25-4.6 (4H), 4.75 (1H), 6.1 (2H), 6.6 (1H), 6.9 (3H), 7.8 (2H), 8.3 (2H) ppm.

MS: m/e = 382 (M^+)

Example 12

4-(N-(4-Methoxy)benzyl-N-methylaminomethyl)benzoic acid N-(3-butan-1-al-2-yl)amide

MS: m/e = 368 (M^+)

Example 13

4-(N-(3,4-Dioxomethylene)benzyl-N-methylaminomethyl)-benzoic acid N-(3-cyclohexylpropan-1-al-2-yl)amide

^{1}H-NMR (CF_3COOD): δ = 1.0-2.0 (13H), 2.9 (3H), 4.3-4.9 (4H), 6.1 (2H), 6.6 (1H), 6.9 (3H), 7.8 (2H), 8.3 (2H) ppm.

MS: m/e = 436 (M^+)

Example 14

4-(N-(4-Benzyl-N-methylaminomethyl)benzoic acid N-(3-cyclohexylpropan-1-al-2-yl)amide

^{1}H-NMR (d_6-DMSO): δ = 1.0-1.8 (13H), 2.1 (3H), 3.4 (2H), 3.5 (2H), 4.3 (1H), 7.1-7.4 (5H), 7.5 (2H), 7.8 (2H), 8.8 (1H), 9.5 (1H) ppm.

Example 15

4-(N-(4-Methoxy)benzyl-N-methylaminomethyl)benzoic acid N-(3-cyclohexylpropan-1-al-2-yl)amide

^{1}H-NMR ($CDCl_3$): δ = 1.0-1.8 (13H), 2.1 (3H), 3.4 (2H), 3.5 (2H), 3.7 (3H), 4.3 (1H), 6.8 (2H), 7.25 (2H), 7.5 (2H), 7.9 (2H), 8.8 (1H), 9.5 (1H) ppm.

Example 16

4-((2-Phenylpyrrolid-1-yl)methyl)benzoic acid N-(3-cyclohexylpropan-1-al-2-yl)amide

MS: m/e = 420 (M^+)

Example 17

4-((2-Phenylpyrrolid-1-yl)methyl)benzoic acid N-(3-butan-1-al-2-yl)amide

MS: m/e = 364 (M^+)

Example 18

4-((2-Phenylpyrrolid-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

MS: m/e = 412 (M^+)

Example 19

4-((1,2,3,4-Dihydroquinolin-1-yl)methyl)benzoic acid N-(3-cyclohexylpropan-1-al-2-yl)amide

^{1}H-NMR ($CDCl_3$): δ = 1.0-1.9 (13H), 2.0 (2H), 2.8 (2H), 3.3 (2H), 4.5 (2H), 4.8 (1H), 6.4 (1H), 6.5 (2H), 7.0 (2H), 7.4 (2H), 7.8 (2H), 9.7 (1H) ppm.

MS: m/e = 404 (M^+)

Example 20

4-((1,2,3,4-Dihydroquinolin-1-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

^{1}H-NMR (d_6-DMSO): δ = 1.9 (2H), 2.75 (2H), 2.9 (1H), 3.3 (1H), 3.4 (2H), 4.4 (1H), 4.5 (2H), 6.3 (2H), 6.8 (2H), 7.1-7.25 (5H), 7.3 (2H), 7.7 (2H), 8.8 (1H), 9.5 (1H) ppm.

MS: m/e = 398 (M^+)

Example 21

4-((1,2,3,4-Dihydroquinolin-1-yl)methyl)benzoic acid N-(3-butan-1-al-2-yl)amide

^{1}H-NMR (d_6-DMSO): δ = 0.9 (3H), 1.2-2.0 (6H), 2.7 (2H), 3.3 (2H), 4.2 (1H), 4.5 (2H), 6.4 (2H), 6.8 (2H), 7.3 (2H), 7.8 (2H), 8.8 (1H), 9.5 (1H) ppm.

MS: m/e = 350 (M^+)

Example 22

4-((1,2,3,4-Dihydroisoquinolin-2-yl)methyl)benzoic acid N-(3-cyclohexylpropan-1-al-2-yl)amide

^{1}H-NMR (d_6-DMSO): δ = 0.9-1.8 (13H), 2.7-2.9 (4H), 3.6 (2H), 3.75 (2H), 4.4 (1H), 6.9-7.1 (4H), 7.4 (2H), 7.8 (2H), 8.8 (1H), 9.5 (1H) ppm.

MS: m/e = 404 (M^+)

Example 23

4-((1,2,3,4-Dihydroisoquinolin-2-yl)methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

^{1}H-NMR (d_6-DMSO): δ = 2.7 (2H), 2.8 (2H), 2.9 (1H), 3.2 (1H), 3.5 (2H), 3.7 (2H), 4.5 (1H), 6.9-7.1 (4H), 7.2-7.3 (5H), 7.5 (2H), 7.75 (2H), 8.8 (1H), 9.5 (1H) ppm.

MS: m/e = 398 (M^+)

Example 24

4-((1,2,3,4-Dihydroisoquinolin-2-yl)methyl)benzoic acid N-(3-butan-1-al-2-yl)amide hydrochloride

^{1}H-NMR (d_6-DMSO): δ = 0.9 (3H), 1.2-2.0 (4H), 3.0 (1H), 3.3 (2H), 3.6 (1H), 4.1-4.6 (5H), 7.2 (4H), 7.8 (2H), 8.0 (2H), 9.0 (1H), 9.5 (1H), 11.75 (1H) ppm.

Example 25

4-((6,7-Dimethoxy-1,2,3,4-dihydroisoquinolin-2-yl)-methyl)benzoic acid N-(3-cyclohexylpropan-1-al-2-yl)-amide

^{1}H-NMR (d_6-DMSO): δ = 0.9-1.9 (13H), 2.7 (4H), 3.4 (2H), 3.6 (3H), 3.65 (2H), 3.7 (3H), 4.3 (1H), 6.5 (1H), 6.6 (1H), 7.5 (2H), 7.8 (2H), 8.8 (1H), 9.5 (1H) ppm.

MS: m/e = 464 (M^+)

Example 26

4-((6,7-Dimethoxy-1,2,3,4-dihydroisoquinolin-2-yl)-methyl)benzoic acid N-(3-phenylpropan-1-al-2-yl)amide

^{1}H-NMR (d_6-DMSO): δ = 2.7 (4H), 2.9 (1H), 3.25 (1H), 3.6 (6H), 3.7 (2H), 4.5 (1H), 6.6 (1H), 6.7 (1H), 7.2-7.3 (5H), 7.4 (2H), 7.8 (2H), 8.9 (1H), 9.6 (1H) ppm.

MS: m/e = 458 (M^+)

Example 27

4-((6,7-Dimethoxy-1,2,3,4-dihydroisoquinolin-2-yl)-methyl)benzoic acid N-(3-butan-1-al-2-yl)amide

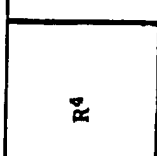
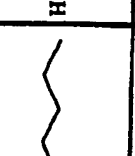
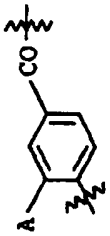
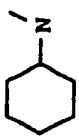
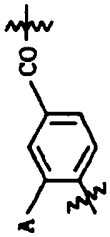
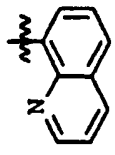
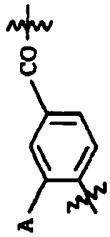
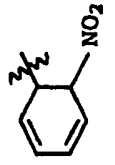
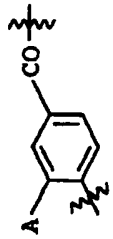
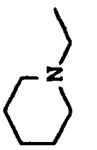
^{1}H-NMR (d_6-DMSO): δ = 0.9 (3H), 1.4 (2H), 1.5-1.8 (2H), 2.7 (4H), 3.4 (2H), 3.7 (3H), 3.75 (3H), 3.8 (2H), 4.3 (1H), 6.6 (1H), 6.7 (1H), 7.4 (2H), 7.8 (2H), 8.8 (1H), 9.5 (1H) ppm.

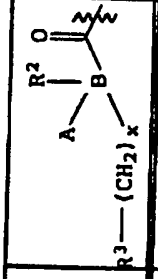
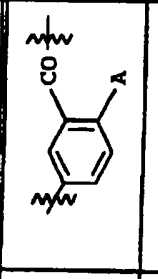
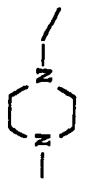
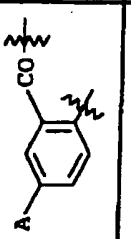
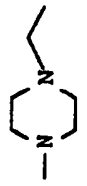
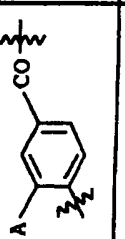
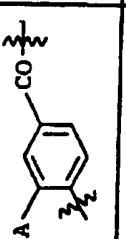
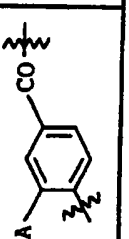
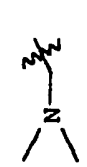
MS: m/e = 410 (M^+)

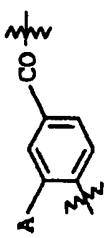
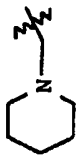
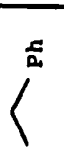
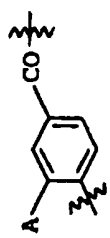
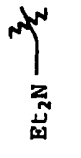
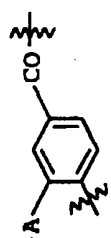
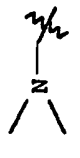
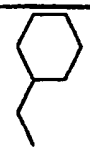
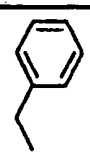
Example 28

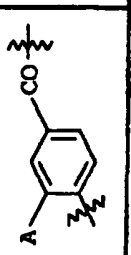
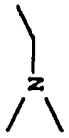
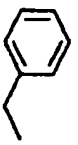
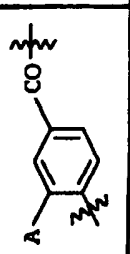
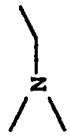
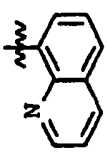
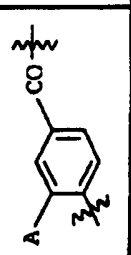
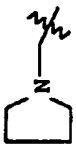
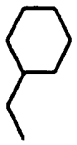
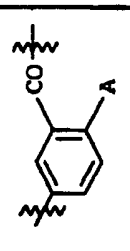
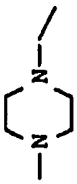
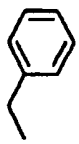
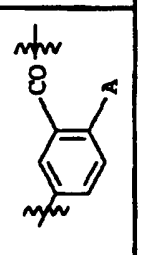
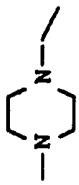
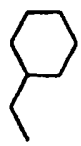
2-((1,2,3,4-Dihydroquinolin-1-yl)methyl)benzoic acid N-(3-butan-1-al-2-yl)amide

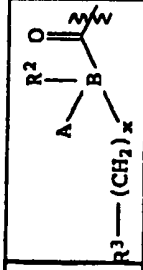
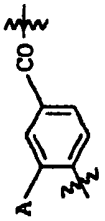
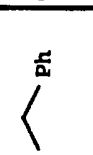
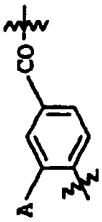
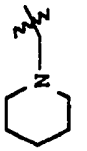
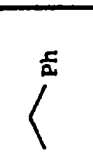
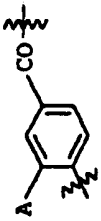
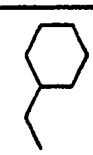
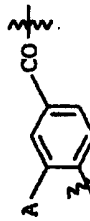
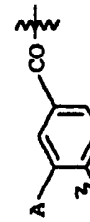
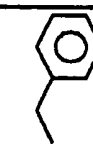
MS: m/e = 441 (M^+)

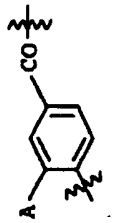
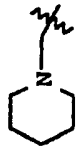
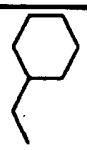
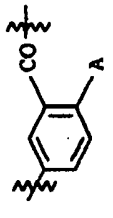
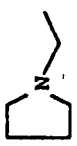
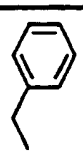
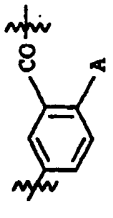
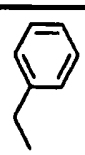
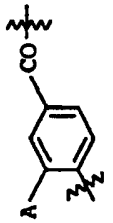
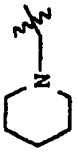
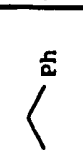
No.	R^1	A	R^2			R^4	R^5
1	Bu	SO_2NH	H				H
2	2-Py	SO_2NH	H				H
3		SO_2NH	H		Me_2N		H
4		SO_2NH	H			Ph	H

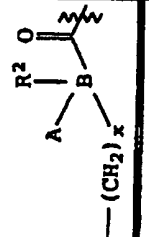
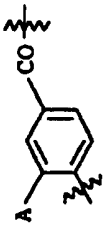
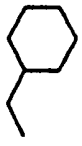
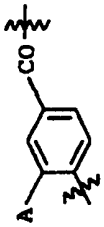
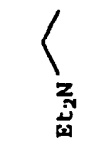
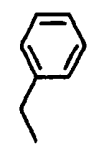
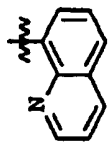
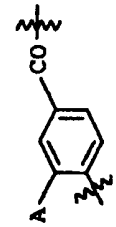
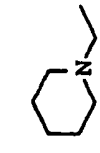
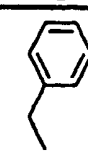
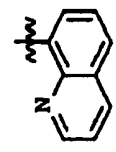
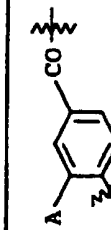
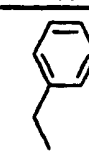
No.	R^1	A	R^2			R^4	R^5
5	Ph	CH_2O	H				H
6	2-Py	CH_2O	H				H
7	Bu	SO_2NH	H				H
8	Naphth	SO_2NH	H				H
9	Naphth	SO_2NH	H				$CONH_2$

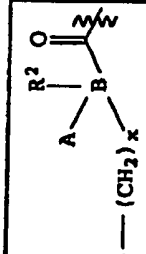
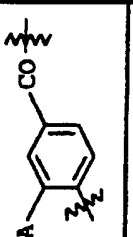
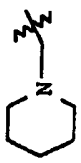
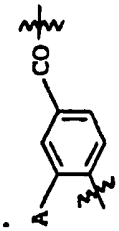
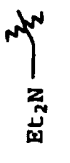
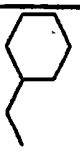
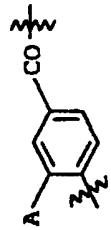
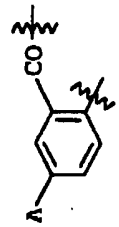
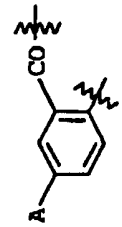
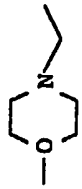
No.	R^1	A	R^2	R^2 O, A, B, R^3—$(CH_2)_x$	R^3—$(CH_2)_x$—	R^4	R^5
10	Ph	SO_2NH	H				H
11	Bu	SO_2NH	H				$CONH_2$
12	Naphth	SO_2NH	H				$CONH_2$
13	Ph	-O-	H				H
14	Ph	-S-	H				$CONH_2$

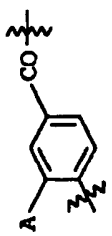
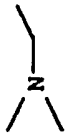
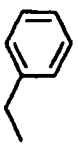
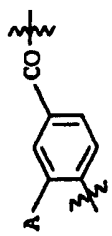
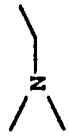
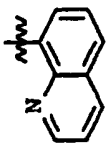
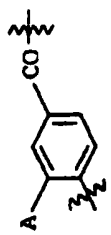
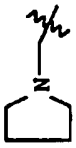
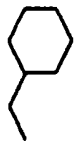
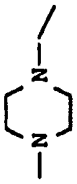
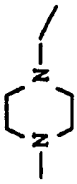
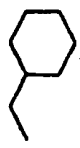
No.	R^1	A	R^2	R^2 O / A / B / R^3—$(CH_2)_x$	R^3—$(CH_2)_x$—	R^4	R^5
15	2-Py	SO_2NH	H				$CONH_2$
16	2-Py	SO_2NH	H				H
17		SO_2NH	H				H
18	Ph	-O-	H				H
19	Ph	-S-	H				$CONH_2$

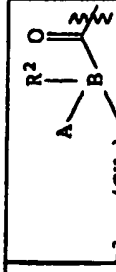
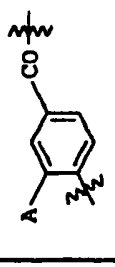
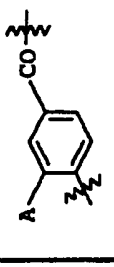
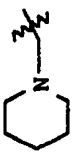
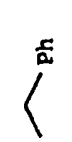
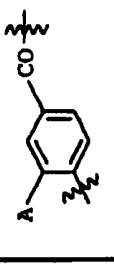
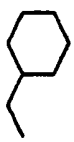
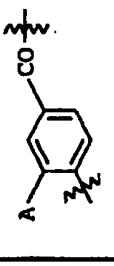
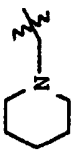
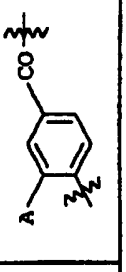
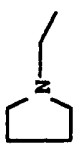
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
20	Bu	SO_2NH	H				$CONH_2$
21	Naphth	SO_2NH	H				H
22	Ph	SO_2NH	H		Et_2N		H
23	Bu	SO_2NH	H				$CONH_2$
24	2-Py	SO_2NH	H				H

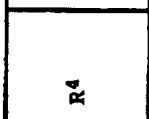
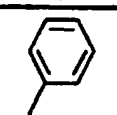
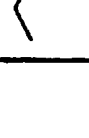
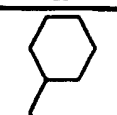
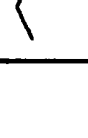
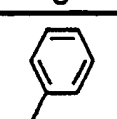
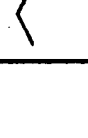
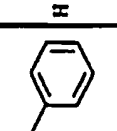
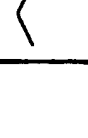
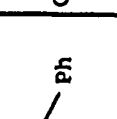
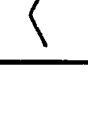
No.	R^1	A	R^2	$R^3-(CH_2)_x-B(R^2)-A-(CH_2)_x-R^3$	$R^3-(CH_2)_x-$	R^4	R^5
25	Ph	-O-	H				$CONH_2$
26	2-Py	SO_2NH	H				H
27	Ph	-O-	H				$CONH_2$
28	Ph	-O-	H				H
29	Naphth	SO_2NH	H				$CONH_2$

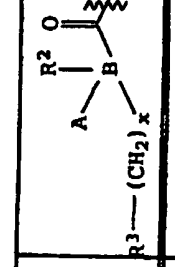
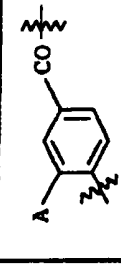
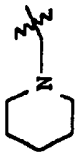
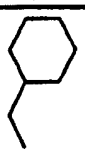
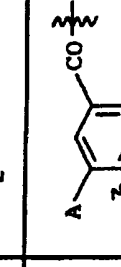
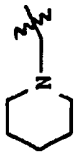
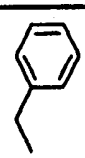
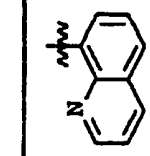
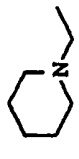
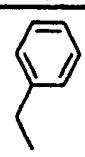
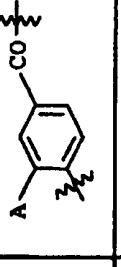
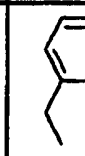
No.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
30	Bu	SO_2NH	H				H
31	2-Py	SO_2NH	H				$CONH_2$
32	Ph	-O-	H				H
33		SO_2NH	H				$CONH_2$
34		SO_2NH	H				H

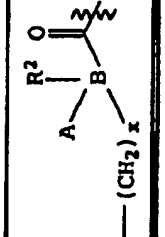
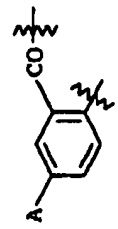
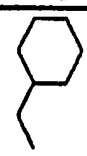
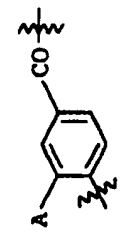
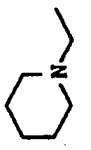
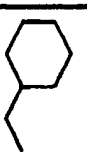
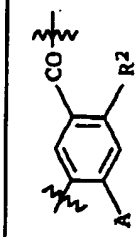
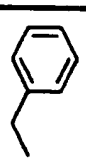
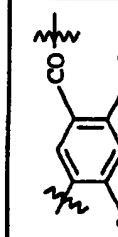
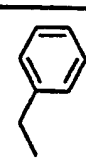
No.	R^1	A	R^2			R^4	R^5
10	Ph	SO_2NH	H				H
11	Bu	SO_2NH	H				$CONH_2$
12	Naphth	SO_2NH	H				$CONH_2$
13	Ph	-O-	H				H
14	Ph	-S-	H				$CONH_2$

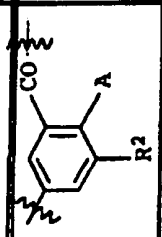
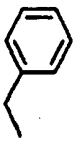
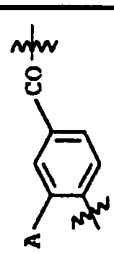
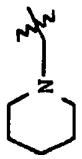
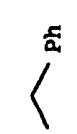
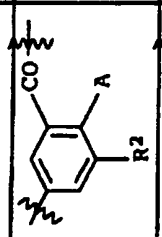
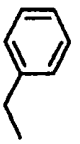
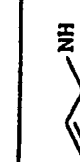
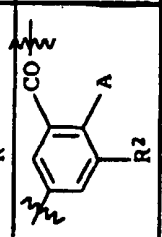
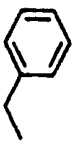
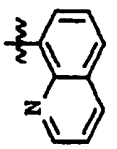
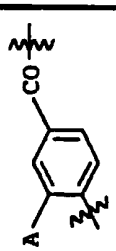
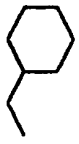
No.	R^1	A	R^2	R^2 O / A–B–$(CH_2)_x$–R^3	R^3—$(CH_2)_x$—	R^4	R^5
15	2-Py	SO_2NH	H				$CONH_2$
16	2-Py	SO_2NH	H				H
17		SO_2NH	H				H
18	Ph	-O-	H				H
19	Ph	-S-	H				$CONH_2$

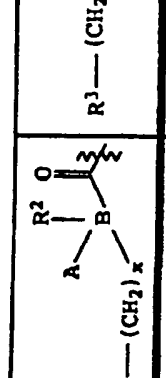
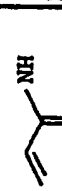
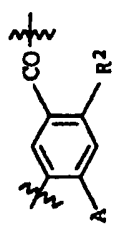
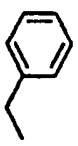
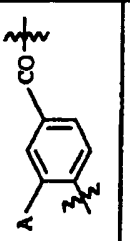
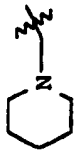
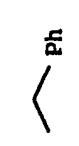
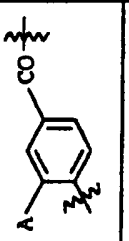
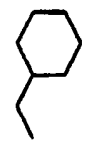
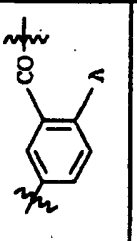
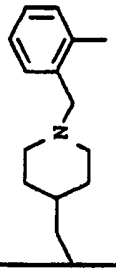
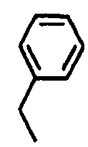
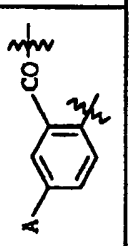
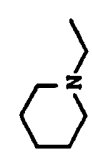
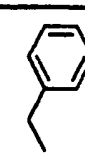
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
20	Bu	SO_2NH	H				$CONH_2$
21	Naphth	SO_2NH	H				H
22	Ph	SO_2NH	H		Et_2N		H
23	Bu	SO_2NH	H				$CONH_2$
24	2-Py	SO_2NH	H				H

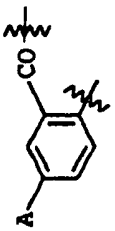
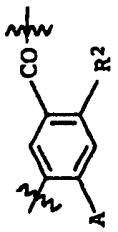
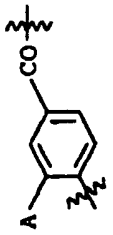
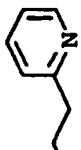
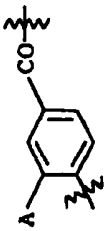
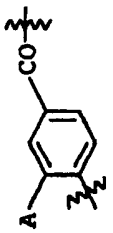
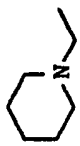
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
25	Ph	-O-	H				$CONH_2$
26	2-Py	SO_2NH	H				H
27	Ph	-O-	H				$CONH_2$
28	Ph	-O-	H				H
29	Naphth	SO_2NH	H				$CONH_2$

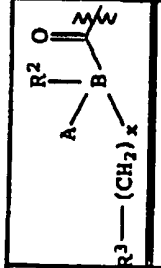
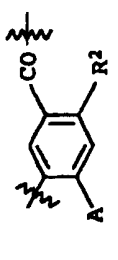
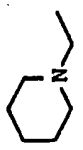
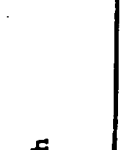
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
30	Bu	SO_2NH	H				H
31	2-Py	SO_2NH	H				$CONH_2$
32	Ph	-O-	H		Et_2N		H
33		SO_2NH	H				$CONH_2$
34		SO_2NH	H				H

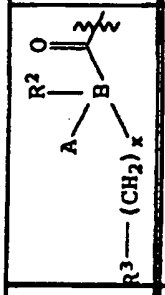
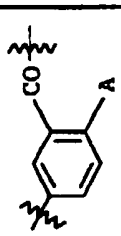
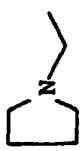
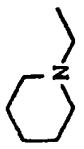
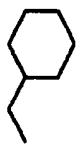
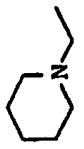
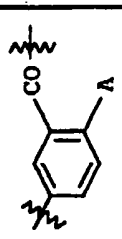
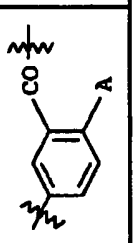
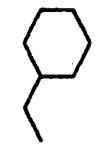
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
35	Ph	-O-	H		Et_2N—		$CONH_2$
36	Ph	-O-	H		Et_2N—		
37		SO_2NH	H				
38	Ph	CONH	MeO		Me_2N—		H
39	Naphth	CONH	MeO		Et_2N—		H

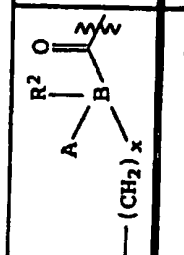
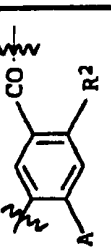
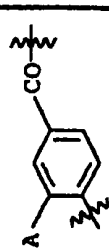
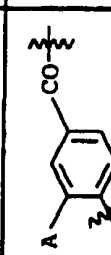
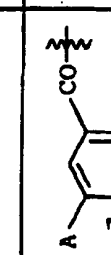
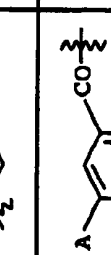
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
40	Ph	CONH	Et		Me_2N		H
41	Bu	SO_2NH	H				H
42	Naphth	CONH	Et		Et_2N		H
43	Ph		Et		Me_2N		H
44		SO_2NH	H		Et_2N		$CONH_2$

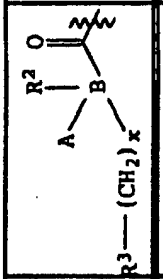
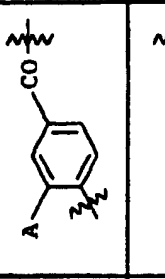
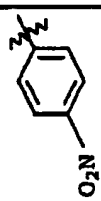
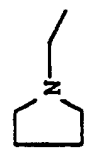
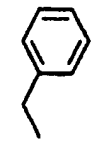
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
45	Ph		MeO		Me_2N		H
46	Bu	SO_2NH	H				$CONH_2$
47	Naphth	SO_2NH	H				H
48	H	m=o=O	H				H
49	Ph	-O-	H				H

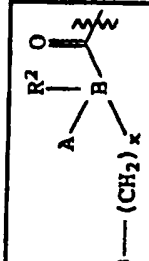
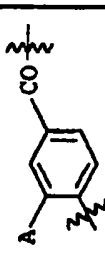
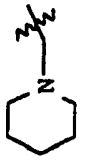
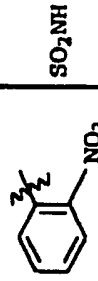
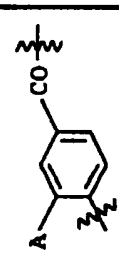
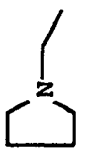
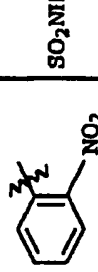
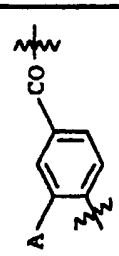
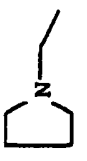
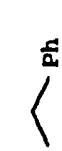
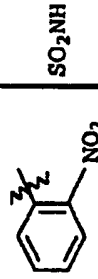
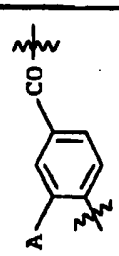
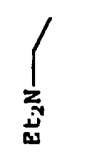
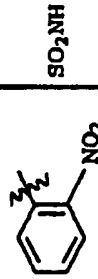
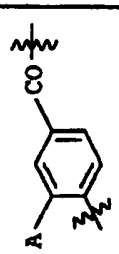
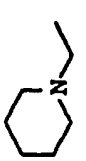
No.	R^1	A	R^2	R^2 O B A $(CH_2)_x$ R^3	R^3—$(CH_2)_x$—	R^4	R^5
50	Ph	-O-	H				$CONH_2$
51	Naphth	CONH	MeO				$CONH_2$
52	Bu	SO_2NH	H				
53	Ph	SO_2NH	H				$CONH_2$
54	2-Py	SO_2NH	H				H

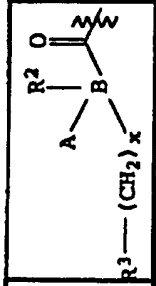
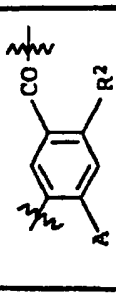
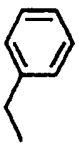
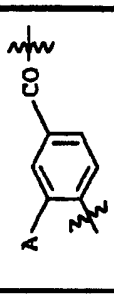
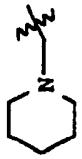
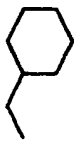
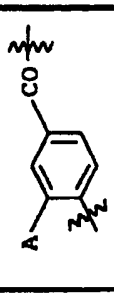
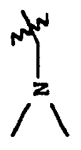
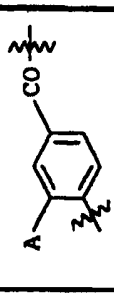
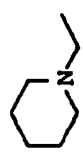
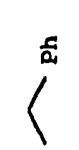
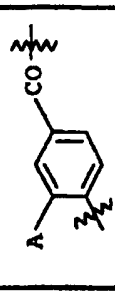
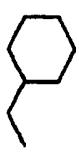
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
55	Ph	CONH	MeO				$CONH_2$
56	Bu	SO_2NH	H				H
57		SO_2NH	H				$CONH_2$
58		SO_2NH	H				H
59		SO_2NH	H				H

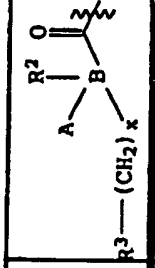
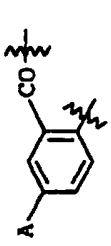
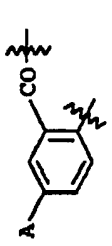
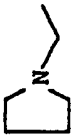
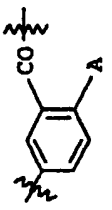
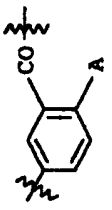
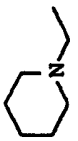
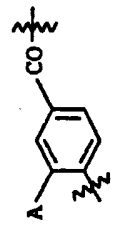
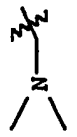
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
60	Ph	CONH	Et				$CONH_2$
61	Ph	O	H				H
62	Ph	O	H				H
63	Ph	O	H		Me_2N		$CONH_2$
64	Ph	O	H		Me_2N		$CONH_2$

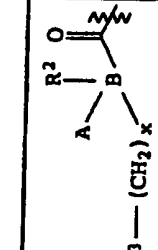
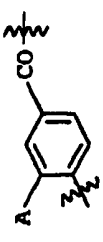
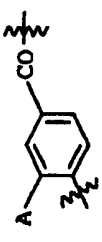
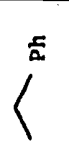
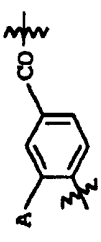
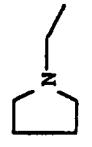
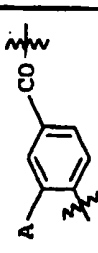
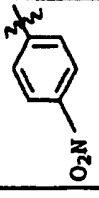
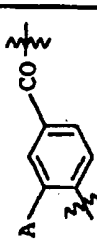
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
65	Ph	CONH	MeO				$CONH_2$
66	Ph	SO_2NH	H				
67	Ph	SO_2NH	H		Et_2N		$CONH_2$
68	Ph	SO_2NH	H		Et_2N		H
69	Bu	SO_2NH	H				$CONH_2$

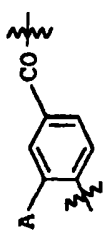
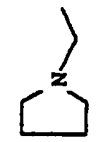
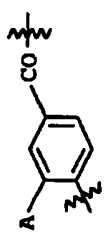
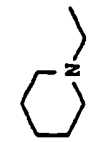
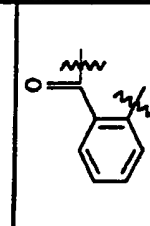
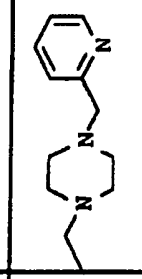
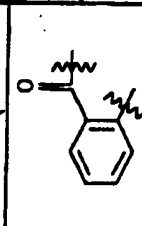
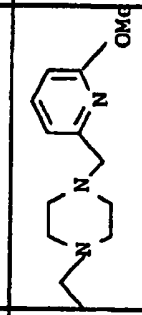
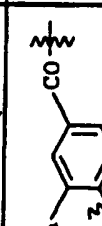
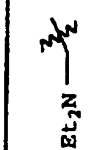
No.	R^1	A	R^2			R^4	R^5
70		SO_2NH	H				H
71		SO_2NH	H		Et_2		$CONH_2$
72	Ph	CONH	Et				H
73	Bu	SO_2NH	H				
74	Ph	SO_2NH	H		Et_2N		$CONH_2$

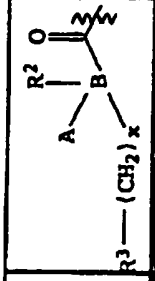
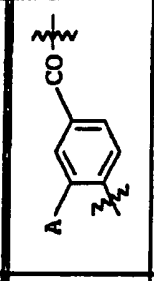
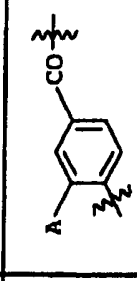
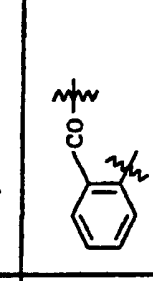
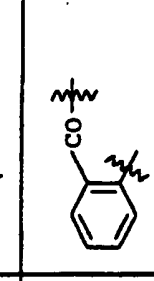
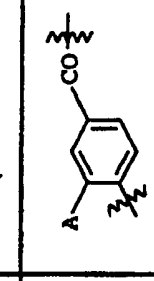
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
75	Naphtha	SO_2NH	H				H
76		SO_2NH	H				H
77		SO_2NH	H				$CONH_2$
78		SO_2NH	H				$CONH_2$
79		SO_2NH	H				$CONH_2$

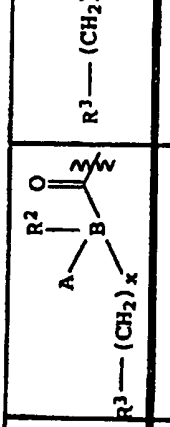
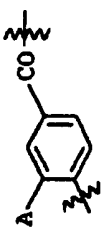
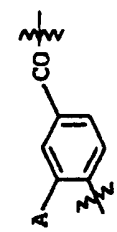
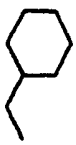
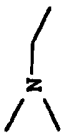
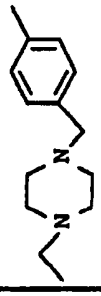
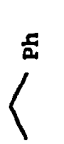
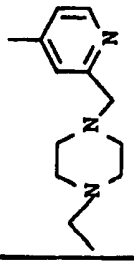
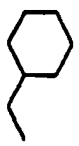
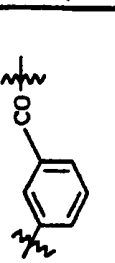
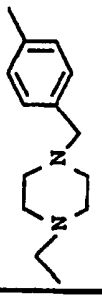
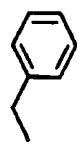
No.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
80	Naphth	CONH	MeO				H
81	Naphth	SO_2NH	H				$CONH_2$
82	Naphth	SO_2NH	H				H
83		SO_2NH	H				$CONH_2$
84		SO_2NH	H		$Me_2N—$		$CONH_2$

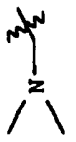
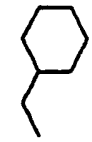
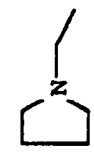
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
85	Ph	O	H				$CONH_2$
86	Ph	S	H				H
87	Ph	O	H		Me_2N		H
88	Ph	O	H				$CONH_2$
89	Ph	SO_2NH	H				$CONH_2$

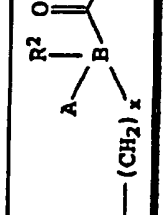
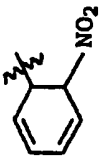
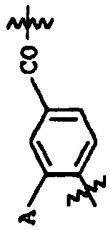
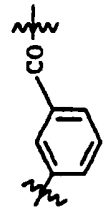
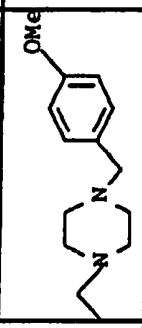
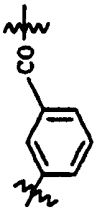
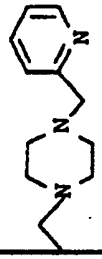
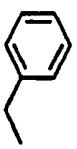
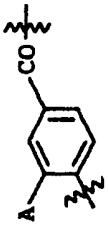
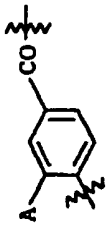
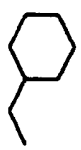
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
90	Naphth	SO_2NH	H				H
91	2-Py	SO_2NH	H				H
92	2-Py	SO_2NH	H				$CONH_2$
93		SO_2NH	H		Me_2N		$CONH_2$
94		SO_2NH	H		Et_2N		H

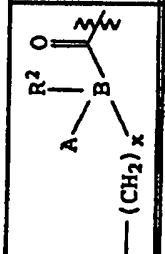
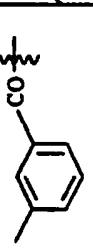
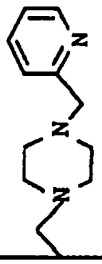
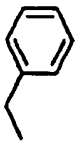
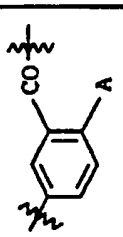
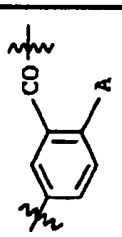
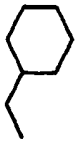
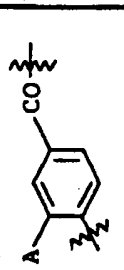
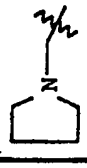
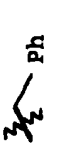
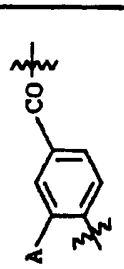
No.	R^1	A	R^2	R^2 A B $(CH_2)_x$ R^3	R^3—$(CH_2)_x$—	R^4	R^5
95		SO_2NH	H				$CONH_2$
96		SO_2NH	H				H
97	H	m=O=O	H				
98	H	m=O=O	H				$CONH_2$
99	Bu	SO_2NH	H		Et_2N— 		$CONH_2$

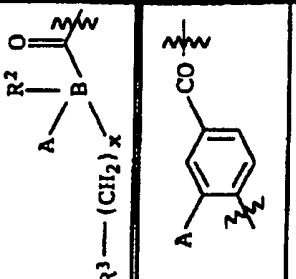
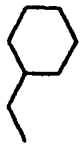
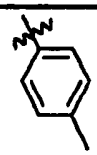
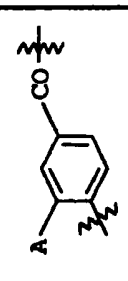
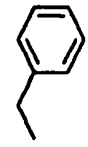
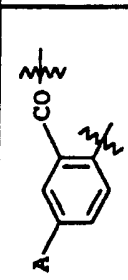
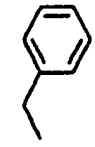
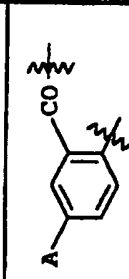
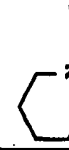
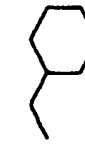
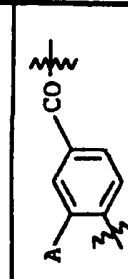
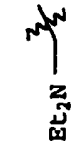
No.	R^1	A	R^2			R^4	R^5
100	Ph	SO_2NH	H				H
101	2-Py	SO_2NH	H				$CONH_2$
102	H	m=o=O	H				H
103	H	m=o=O	H				H
104	Bu	SO_2NH	H				

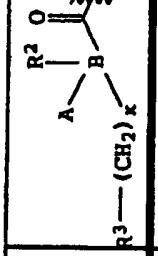
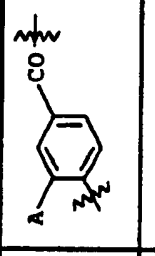
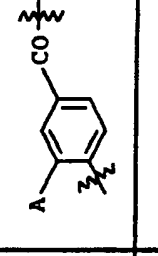
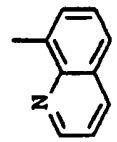
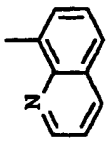
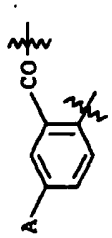
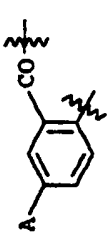
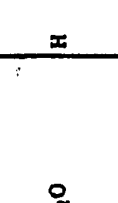
No.	R^1	A	R^2			R^4	R^5
105	Ph	SO_2NH	H				H
106	2-Py	SO_2NH	H				$CONH_2$
107	H	m=o=O	H				$CONH_2$
108	H	m=o=O	H				$CONH_2$
109	H	m=o=O	H				H

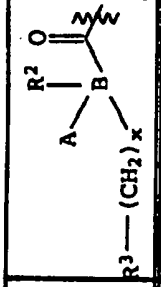
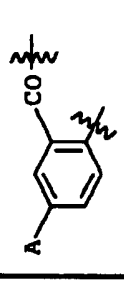
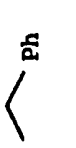
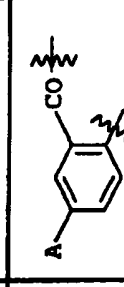
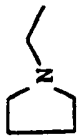
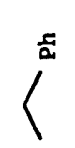
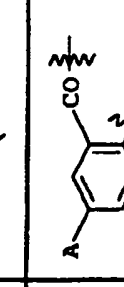
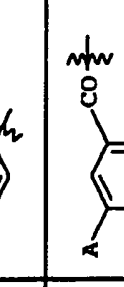
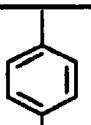
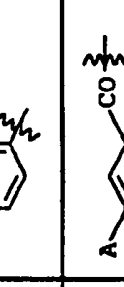
No.	R^1	A	R^2	R^2 O / A / B / R^3—$(CH_2)_x$	R^3—$(CH_2)_x$—	R^4	R^5
110	H	m=o=O	H	CO			H
111	Ph	SO_2NH	H	CO, A		Ph	
112	Ph	SO_2NH	H	CO, A		Ph	$CONH_2$
113	2-Py	SO_2NH	H	CO, A			H
114		SO_2NH	H	CO, A			$CONH_2$

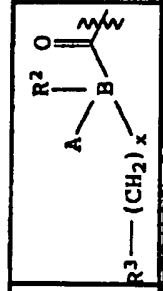
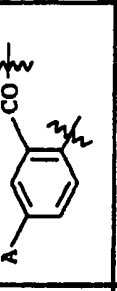
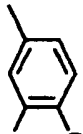
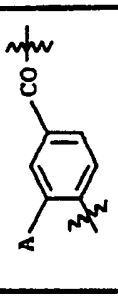
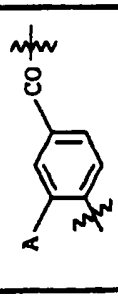
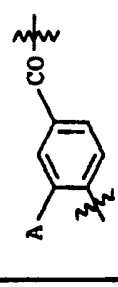
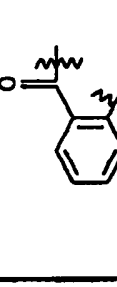
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
115		SO_2NH	H		Et_2N-		H
116	H	m=o=O	H				H
117	H	m=o=O	H				H
118	Ph	SO_2NH	H				H
119	Naphth	SO_2NH	H		Et_2N-		$CONH_2$

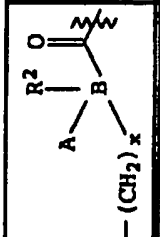
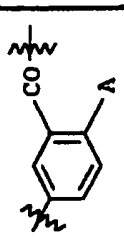
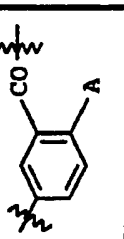
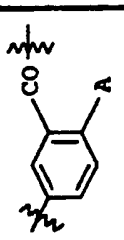
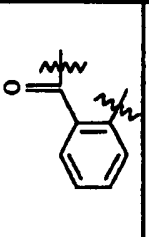
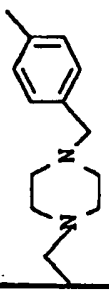
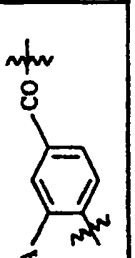
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
120	H	$SONH_2$	H				H
121	Ph	O	H		Me_2N		H
122	Ph	O	H		Me_2N		H
123	Ph	SO_2NH	H				H
124	Naphth	SO_2NH	H				$CONH_2$

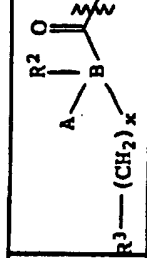
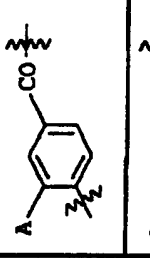
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
125		SO_2NH	H		Me_2N		H
126		SO_2NH	H		Me_2N		$CONH_2$
127	Ph		H				$CONH_2$
128	Ph		H				$CONH_2$
129	Bu	SO_2NH	H				H

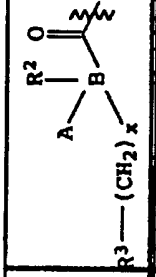
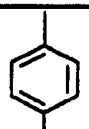
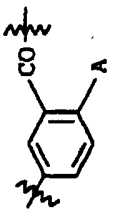
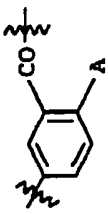
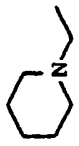
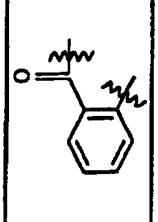
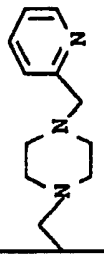
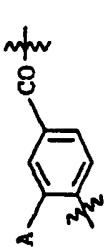
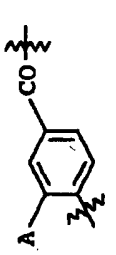
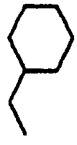
No.	R^1	A	R^2			
130	Ph	SO_2NH	H			$CONH_2$
131		SO_2NH	H			$CONH_2$
132		m=o=O	H			$CONH_2$
133	Ph	CH_2O	H			$CONH_2$
134	2-Py	CH_2O	H			$CONH_2$

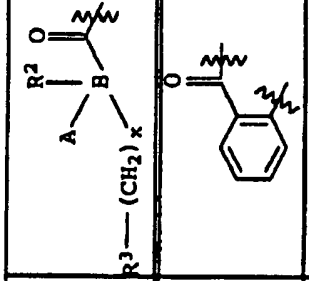
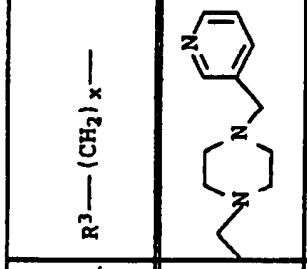
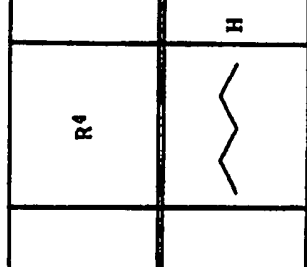
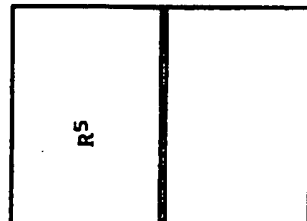
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
135	3-Py	CH_2O	H		Me_2N		$CONH_2$
136	4-Py	CH_2O	H				H
137	2-Tol	CH_2O	H		Me_2N		H
138	3-Tol	CH_2O	H		Et_2N		H
139		CH_2O	H		Me_2N		$CONH_2$

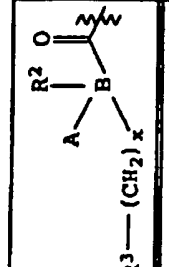
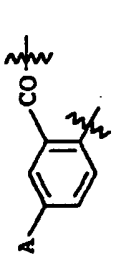
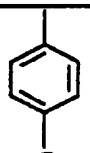
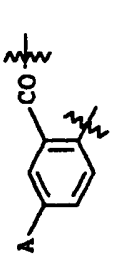
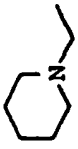
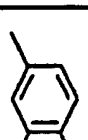
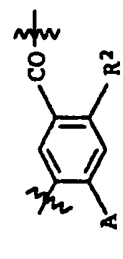
No.	R^1	A	R^2			R^4	R^5
140		CH_2O	H				H
141	Ph	$CONH_2$	H				$CONH_2$
142	Naphth	$CONH_2$	H				$CONH_2$
143	Naphth	$CONH_2$	H				$CONH_2$
144	H	m=o=O	H				$CONH_2$

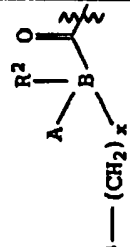
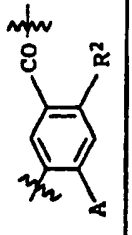
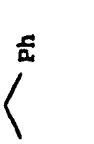
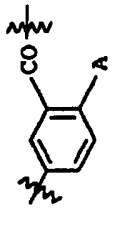
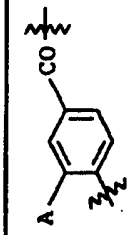
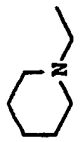
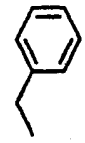
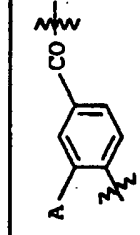
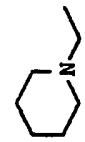
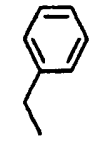
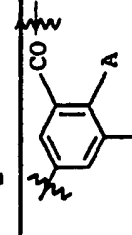
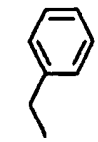
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
145	2-Py	CH_2O	H		Me_2N		H
146	3-Py	CH_2O	H		Et_2N		$CONH_2$
147		CH_2O	H				H
148	H	m=O=O	H				H
149	Ph	CONH	H				H

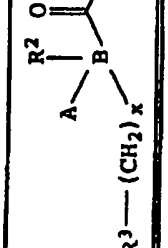
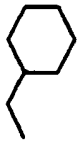
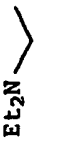
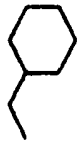
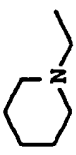
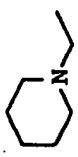
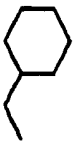
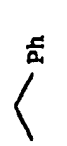
No.	R^1	A	R^2			R^4	R^5
150	Naphth	CONH	H				H
151	Ph		H				H
152	4-Py	CH_2O	H				$CONH_2$
153	2-Tol	CH_2O	H				H
154	3-Tol	CH_2O	H				$CONH_2$

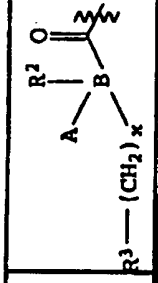
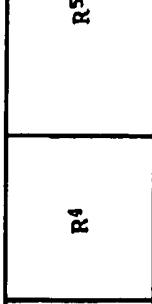
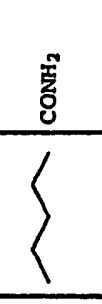
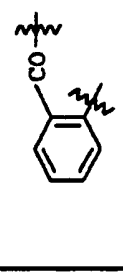
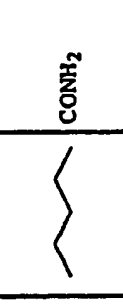
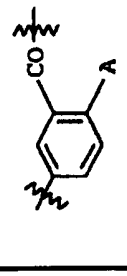
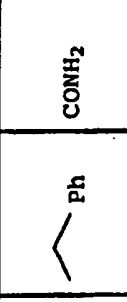
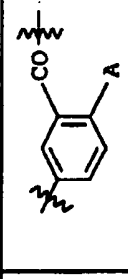
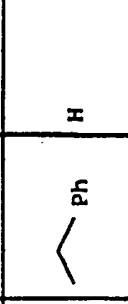
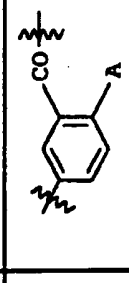
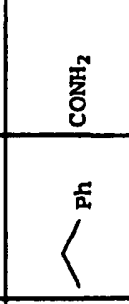
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
155		CH_2O	H		Et_2N		H
156	Ph	CH_2O	H				$CONH_2$
157	H	m=o=O	H				$CONH_2$
158	Naphth	CONH	H		Me_2N		H
159	Ph	CONH	H		Me_2N		$CONH_2$

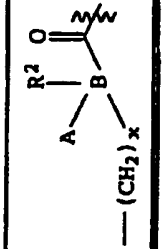
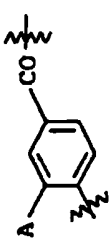
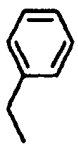
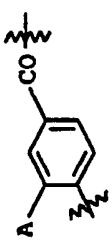
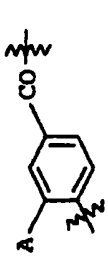
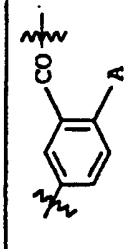
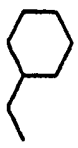
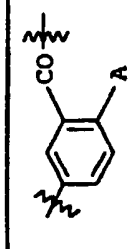
No.	R^1	A	R^2				
160	H	m=o=O	H				
161	Ph	CH_2O	H				
162	2-Py	CH_2O	H				
163	2-Tol	CH_2O	H				
164	3-Py	CH_2O	H				

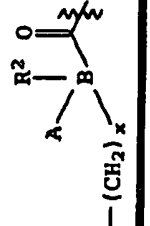
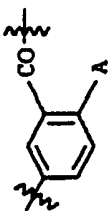
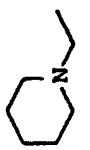
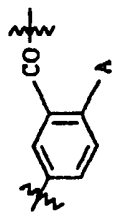
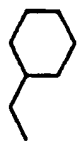
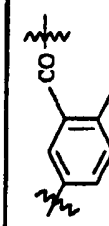
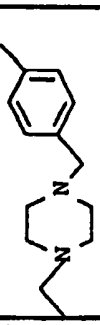
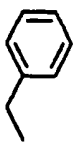
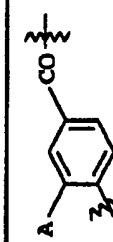
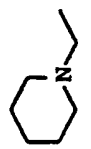
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
165	3-Tol	CH_2O	H		Et_2N		$CONH_2$
166	MeO 	CH_2O	H		Me_2N		H
167		CH_2O	H				H
168	4-Py	CH_2O	H		Et_2N		$CONH_2$
169	Ph	SO_2NH	MeO				H

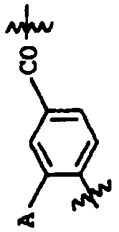
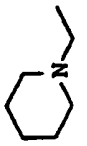
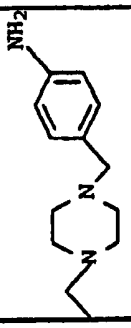
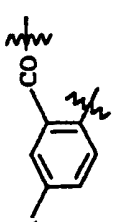
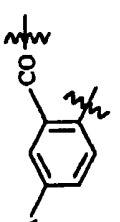
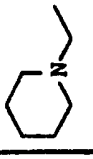
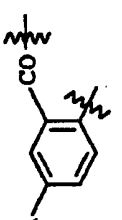
No.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
170	Naphth	SO_2NH	MeO		Me_2N		H
171	3-Tol	CH_2O	H		Me_2N		$CONH_2$
172	Ph	CONH	H				H
173	Naphth	CONH	H				H
174	Bu	SO_2NH	Et		Et_2N		$CONH_2$

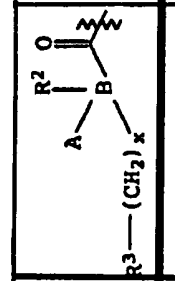
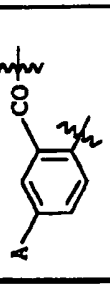
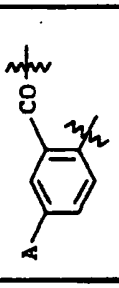
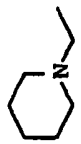
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
175	3-Tol	CH_2O	H				H
176	3-Tol	CH_2O	H				$CONH_2$
177	4-Py	CH_2O	H				H
178	4-Py	CH_2O	H				H
179	Ph	CH_2O	H				$CONH_2$

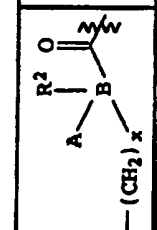
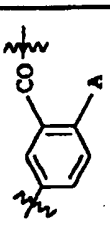
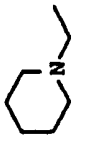
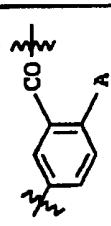
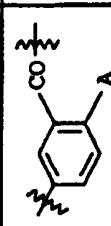
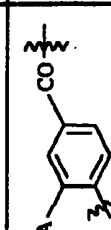
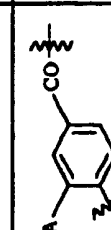
No.	R^1	A	R^2			R^4	R^5
180	Ph	CH_2O	H				$CONH_2$
181	H	m=O=O	H				$CONH_2$
182	Ph	CH_2O	H				$CONH_2$
183	2-Py	CH_2O	H				H
184	MeO—	CH_2O	H				$CONH_2$

No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
185	Ph	CONH	H		Me_2N		$CONH_2$
186	Naphth	CONH	H		Me_2N		H
187	Ph		H		Me_2N		H
188	3-Py	CH_2O	H		Et_2N		H
189	3-Tol	CH_2O	H		Me_2N		H

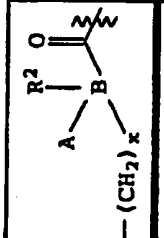
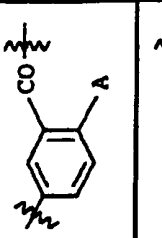
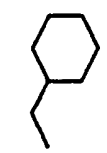
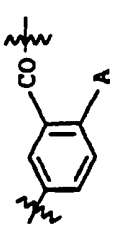
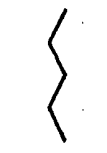
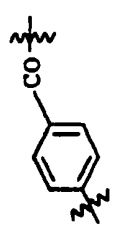
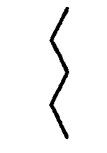
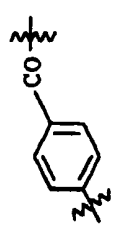
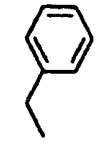
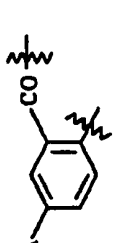
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
190	4-Py	CH_2O	H				$CONH_2$
191	2-Tol	CH_2O	H				$CONH_2$
192		CH_2O	H		Me_2N		H
193	H	m=o=O	H				H
194	Ph	CONH	H				$CONH_2$

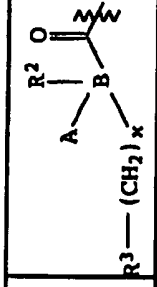
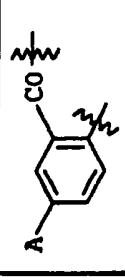
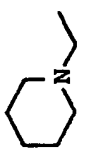
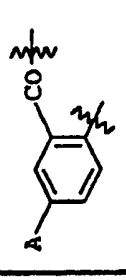
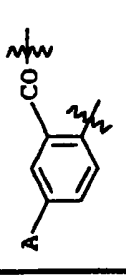
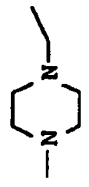
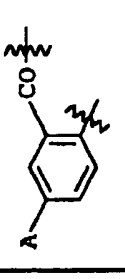
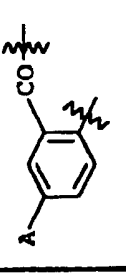
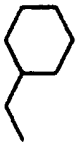
No.	R^1	A	R^2	R^2 O, A, B, $(CH_2)_x$, R^3—$(CH_2)_x$	R^3—$(CH_2)_x$—	R^4	R^5
195	Naphth	CONH	H				$CONH_2$
196	H	m=o=O	H				$CONH_2$
197	2-Py	CH_2O	H		Me_2N		H
198	3-Py	CH_2O	H				$CONH_2$
199	3-Tol	CH_2O	H		Me_2N		$CONH_2$

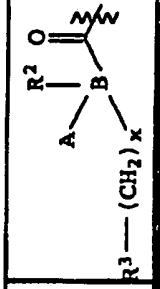
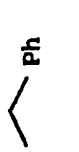
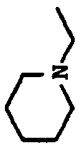
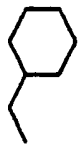
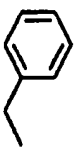
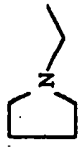
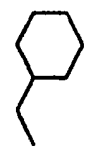
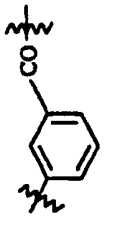
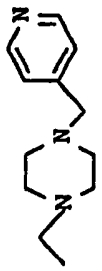
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
200	Ph	CH_2O	H		Et_2N		H
201		CH_2O	H		Me_2N		$CONH_2$
202	4-Py	CH_2O	H		Me_2N	Ph	H
203		CH_2O	H			Ph	$CONH_2$
204	2-Py	CH_2O	H		Me_2N		$CONH_2$

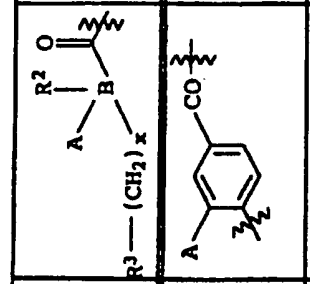
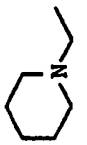
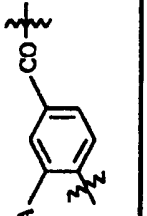
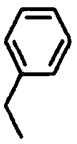
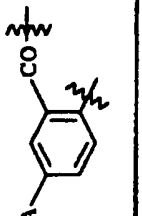
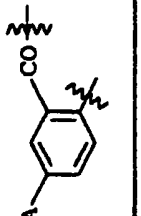
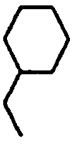
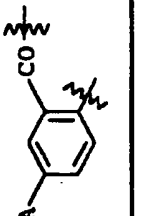
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
205	Ph	CH_2O	H				H
206	2-Py	CH_2O	H		Me_2N		$CONH_2$
207	2-Tol	CH_2O	H		Et_2N		H
208	Ph	CONH	H		Me_2N		H
209	Naphth	CONH	H		Me_2N		$CONH_2$

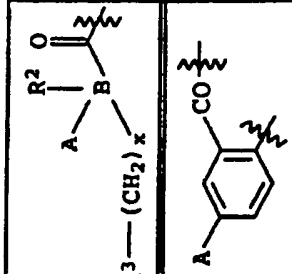
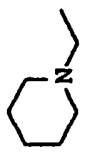
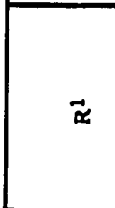
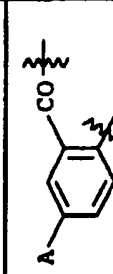
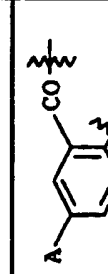
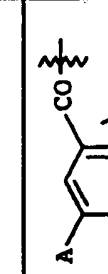
No.	R^1	A	R^2	R^2 O / A / B / A / R^3—$(CH_2)_x$	R^3—$(CH_2)_x$—	R^4	R^5
210	3-Py	CH_2O	H	CO, A	Me_2N	Ph	H
211	4-Py	CH_2O	H	CO, A	N		H
212	MeO	CH_2O	H	CO, A	Et_2N		$CONH_2$
213	Ph	NH, O	H	CO, A	Me_2N		$CONH_2$
214	Ph	CONH	H	CO, A	Me_2N		$CONH_2$

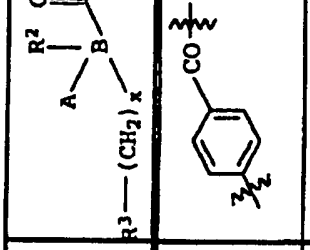
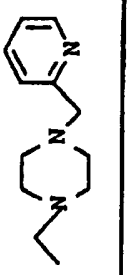
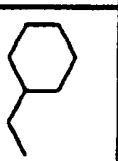
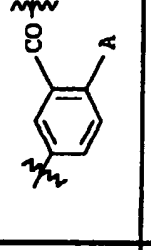
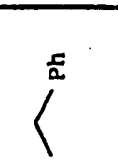
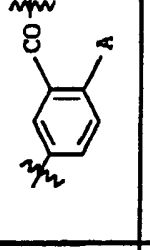
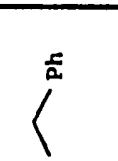
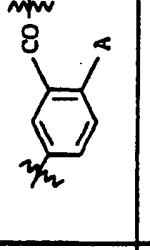
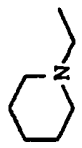
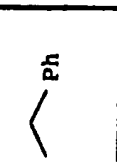
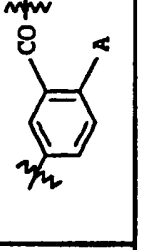
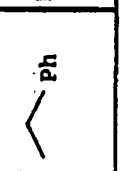
No.	R^1	A	R^2			R^4	R^5
215		CH_2O	H				$CONH_2$
216	3-Tol	CH_2O	H				H
217	H	m=O=O	H				$CONH_2$
218	H	m=O=O	H				H
219	2-Py	CH_2O	H				H

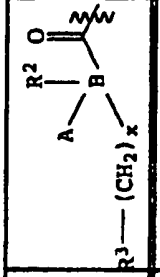
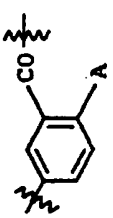
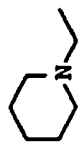
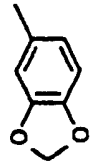
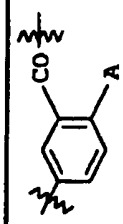
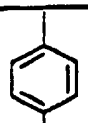
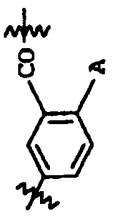
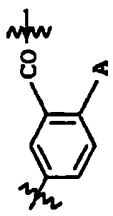
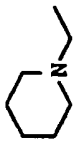
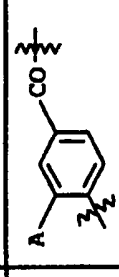
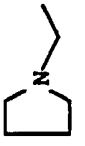
No.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
220	3-Py	CH_2O	H				H
221	2-Tol	CH_2O	H		Me_2N		$CONH_2$
222	4-Tol	CH_2O	H				$CONH_2$
223	4-Py	CH_2O	H				$CONH_2$
224		CH_2O	H		Me_2N		H

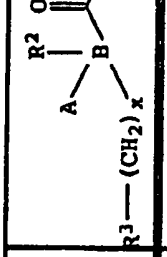
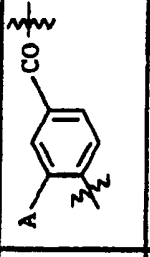
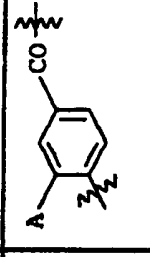
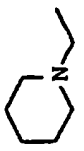
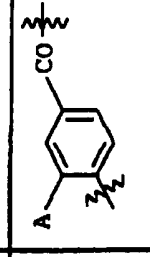
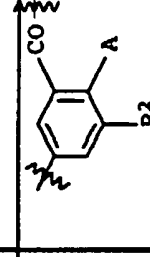
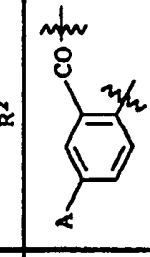
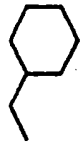
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
225	4-Py	CH_2O	H		Et_2N		H
226	Ph	CH_2O	H				$CONH_2$
227	3-Tol	CH_2O	H		Me_2N		H
228		CH_2O	H				H
229	H	m=o=O	H				$CONH_2$

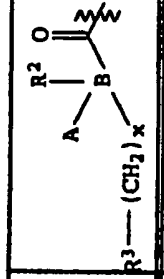
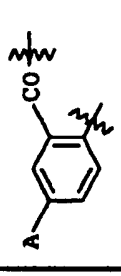
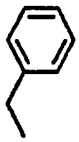
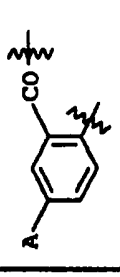
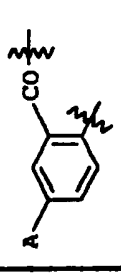
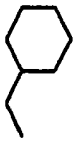
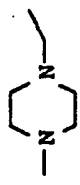
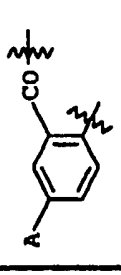
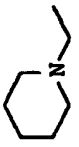
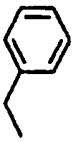
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
230	Ph	CONH	H				$CONH_2$
231	Naphth	CONH	H				$CONH_2$
232	2-Tol	CH_2O	H		Et_2N		H
233	2-Tol	CH_2O	H		Et_2N		$CONH_2$
234	3-Py	CH_2O	H		Me_2N		H

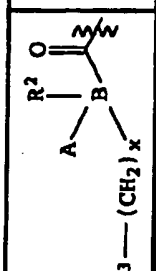
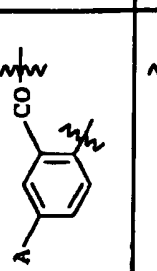
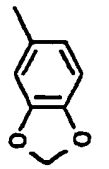
No.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
235	Ph	CH_2O	H				$CONH_2$
236		CH_2O	H				H
237		CH_2O	H		Et_2N		H
238		CH_2O	H		Me_2N		H
239		CH_2O	H		Me_2N		$CONH_2$

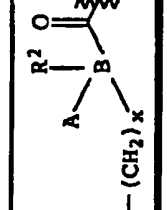
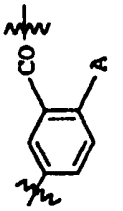
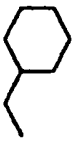
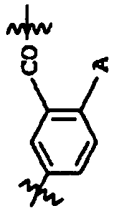
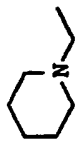
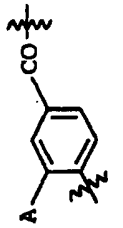
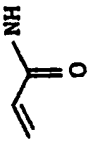
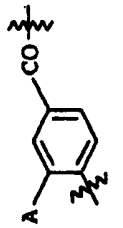
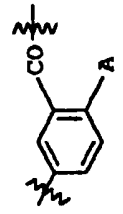
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
240	H	m=o=O	H				
241	Ph	CH_2O	H		Me_2N		H
242	3-Py	CH_2O	H		Me_2N		$CONH_2$
243	4-Py	CH_2O	H				H
244	2-Tol	CH_2O	H		Et_2N		H

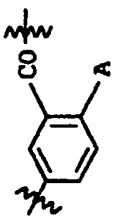
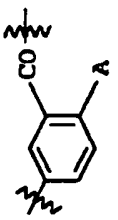
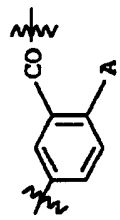
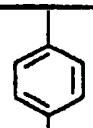
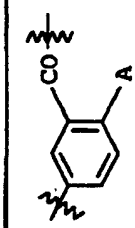
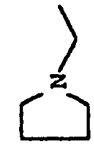
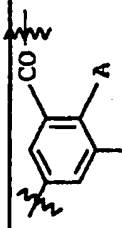
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
245	3-Tol	CH_2O	H				$CONH_2$
246		CH_2O	H		Me_2N		H
247		CH_2O	H		Et_2N		H
248	2-Py	CH_2O	H				$CONH_2$
249	Ph	CONH	H				H

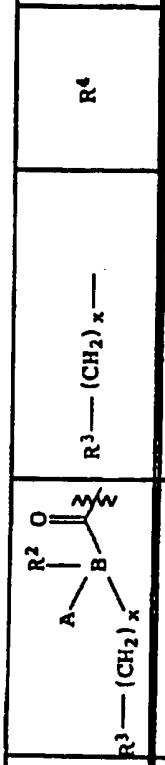
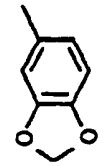
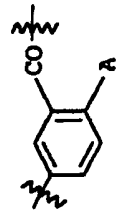
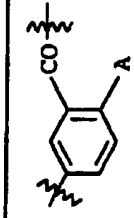
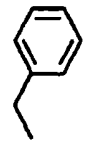
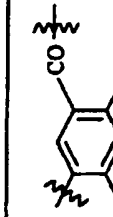
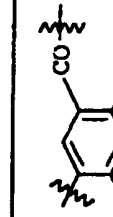
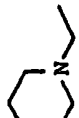
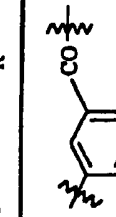
No.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
250	Ph	CONH	H				$CONH_2$
251	Ph	CONH	H				H
252	Naphth	CONH	H				H
253	Ph	SO_2NH	Et		Me_2N		H
254	Ph	CH_2O	H		Et_2N		H

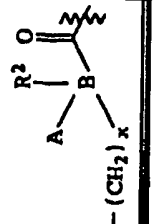
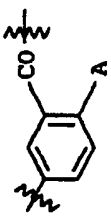
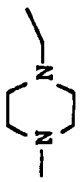
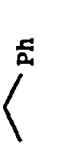
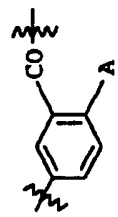
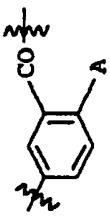
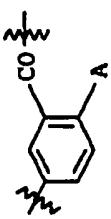
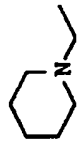
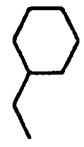
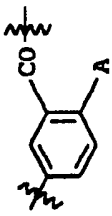
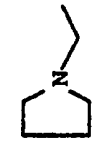
No.	R^1	A	R^2		$R^3—(CH_2)_x—$	R^4	R^5
255	2-Py	CH_2O	H				$CONH_2$
256		CH_2O	H		Me_2N		H
257	3-Py	CH_2O	H				$CONH_2$
258	2-Tol	CH_2O	H				$CONH_2$
259	3-Tol	CH_2O	H				$CONH_2$

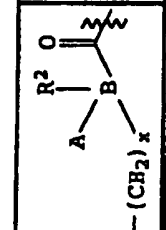
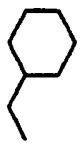
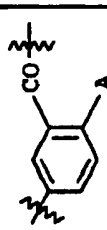
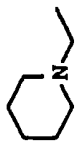
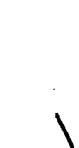
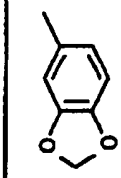
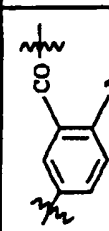
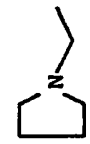
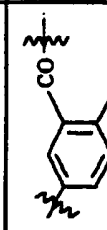
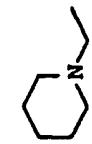
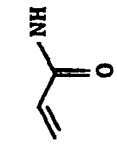
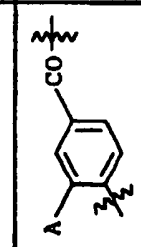
No.	R^1	A	R^2			R^4	R^5
260		CH_2O	H				H
261	4-Py	CH_2O	H				$CONH_2$
262	Ph	CH_2O	H				H
263	Bu	SO_2NH	MeO				H
264	Naphth	SO_2NH	Et				H

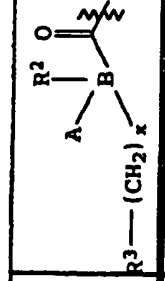
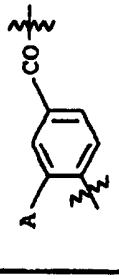
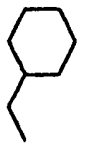
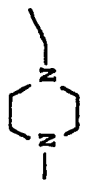
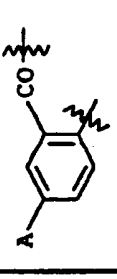
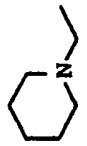
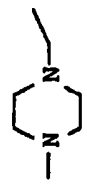
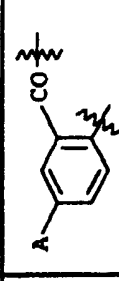
No.	R^1	A	R^2			R^4	R^5
265	4-Py	CH_2O	H		Et_2N		$CONH_2$
266	3-Tol	CH_2O	H			Ph	H
267	Ph	CONH	H		Et_2N	Ph	$CONH_2$
268	Ph		H		Et_2N	Ph	$CONH_2$
269	2-Py	CH_2O	H				$CONH_2$

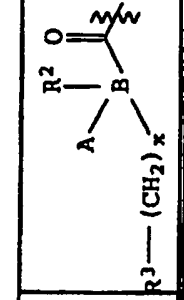
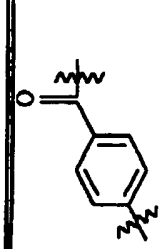
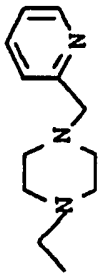
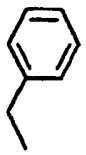
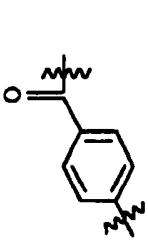
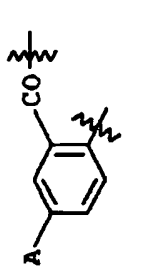
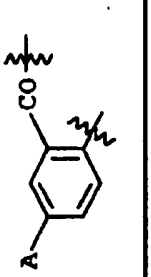
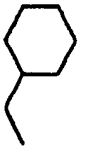
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
270	2-Tol	CH_2O	H		Et_2N	Ph	$CONH_2$
271	Ph	CH_2O	H		Me_2N		H
272	3-Py	CH_2O	H			Ph	$CONH_2$
273		CH_2O	H			Ph	$CONH_2$
274	Ph	SO_2NH	Et		Et_2N	Ph	H

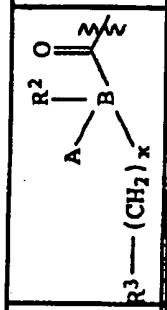
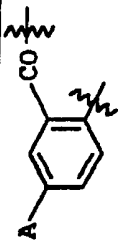
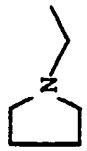
No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
275		CH_2O	H		Et_2N		$CONH_2$
276	Naphth	SO_2NH	Et		Me_2N		$CONH_2$
277	Ph	SO_2NH	MeO		Me_2N	Ph	H
278	Naphth	SO_2NH	MeO			Ph	H
279	Bu	SO_2NH	MeO		Me_2N	Ph	H

No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
280	Ph	CH_2O	H				$CONH_2$
281		CH_2O	H		Et_2N		H
282	Ph	CH_2O	H		Me_2N		$CONH_2$
283		CH_2O	H				H
284	2-Py	CH_2O	H				H

No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
285	2-Py	CH_2O	H		Et_2N		$CONH_2$
286	3-Py	CH_2O	H				H
287		CH_2O	H				$CONH_2$
288	2-Tol	CH_2O	H				H
289	Ph		H		Et_2N		$CONH_2$

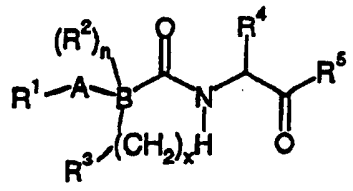
No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
290	Ph	CONH	H		Et_2N		$CONH_2$
291	4-Py	CH_2O	H				H
292	4-Py	CH_2O	H			Ph	$CONH_2$
293	3-Tol	CH_2O	H			Ph	$CONH_2$
294	2-Tol	CH_2O	H		Et_2N		$CONH_2$

No.	R^1	A	R^2		R^3—$(CH_2)_x$—	R^4	R^5
295	H	m=O=O	H				H
296	H	m=O=O	H				H
297	3-Tol	CH_2O	H				H
298	2-Py	CH_2O	H		Me_2N		H

No.	R^1	A	R^2		$R^3-(CH_2)_x-$	R^4	R^5
299		CH_2O	H		Me_2N		$CONH_2$
298	2-Tol	CH_2O	H				H

We claim:

1. An amide of the formula I

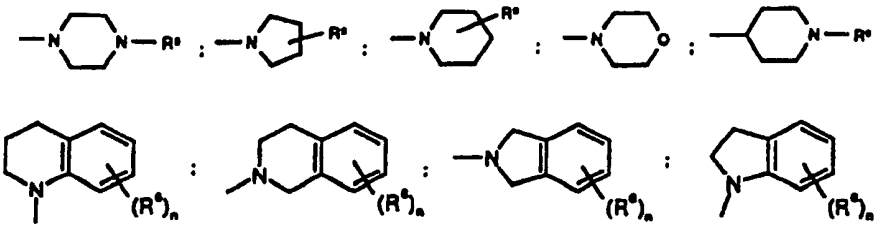


and its tautomeric and isomeric forms, possible enantiomeric and diastereomeric forms, and possible physiologically tolerated salts, in which the variables have the following meanings:

R^1 can be hydrogen, C_1-C_6-alkyl, branched and unbranched, phenyl, naphthyl, quinolyl, pyridyl, pyrimidyl, pyrazyl, pyridazyl, quinazolyl, quinoxalyl, thienyl, benzothienyl, benzofuranyl, furanyl and indolyl, it being possible for the rings also to be substituted by to 3 R^6 radicals, and

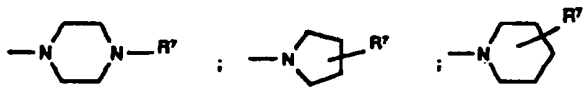
R^2 are hydrogen, C_1-C_6-alkyl, branched or unbranched, O-C_1-C_6-alkyl, branched or unbranched, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkyl-phenyl, C_2-C_6-alkenyl-phenyl, C_2-C_6-alkynyl-phenyl, OH, Cl, F, Br, I, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-alkyl, NHCO-C_1-C_4-alkyl, NHCO-phenyl, $CONHR^9$, $NHSO_2$-C_1-C_4-alkyl, $NHSO_2$-phenyl, SO_2-C_1-C_4-alkyl and SO_2-phenyl, and

R^3 can be NR^7R^8 or a ring such as



R^4 is $-C_1$-C_6-alkyl, branched or unbranched, which may also carry a phenyl, pyridyl, thienyl, cyclohexyl, indolyl or naphthyl ring which is in turn substituted by a maximum of two R^6 radicals, and

R^5 is hydrogen, $COOR^{11}$ and CO-Z in which Z is $NR^{12}R^{13}$ and

 and

R^6 is hydrogen, C_1-C_4-alkyl, branched or unbranched, -O-C_1-C_4-alkyl, OH, Cl, F, Br, I, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-alkyl, -NHCO-C_1-C_4-alkyl, -NHCO-phenyl, -$NHSO_2$-C_1-C_4-alkyl, -$NHSO_2$-phenyl, -SO_2-C_1-C_4-alkyl and -SO_2-phenyl, and

R^7 is hydrogen, C_1-C_6-alkyl, linear or branched, and which may be substituted by a phenyl ring which itself may also be substituted by one or two R^{10} radicals, and

R^8 is hydrogen, C_1-C_6-alkyl, linear or branched, which may be substituted by a phenyl ring which may itself also be substituted by one or two R^{10} radicals, and

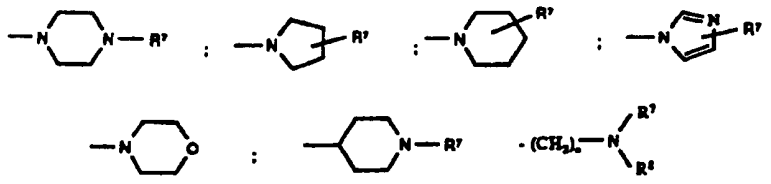
R^9 is hydrogen, C_1-C_6-alkyl, branched or unbranched, which may also carry a sub-

stituent R^{16}, or phenyl, pyridyl, pyrimidyl, pyridazyl, pyrazinyl, pyrazyl, naphthyl, quinolyl, imidazolyl, which may also carry one or two substituents R^{14}, and

R^{10} can be hydrogen, C_1-C_4-alkyl, branched or unbranched, -O-C_1-C_4-alkyl, OH, Cl, F, Br, I, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-alkyl, -NHCO-C_1-C_4-alkyl, -NHCO-phenyl, -$NHSO_2$-C_1-C_4-alkyl, -$NHSO_2$-phenyl, -SO_2-C_1-C_4-alkyl and -SO_2-phenyl

R^{11} is hydrogen, C_1-C_6-alkyl, linear or branched, and which may be substituted by a phenyl ring which may itself also be substituted by one or two R^{10} radicals, and

R^{12} is hydrogen, C_1-C_6-alkyl, branched and unbranched, and



[sic]

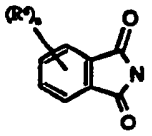
R^{13} is hydrogen, C_1-C_6-alkyl, branched or unbranched, which may also be substituted by a phenyl ring which may also carry an R^{10} radical, and by [lacuna]
and

R^{14} is hydrogen, C_1-C_6-alkyl, branched or unbranched, O-C_1-C_6-alkyl, branched or unbranched, OH, Cl, F, Br, I, CF_3, NO_2, NH_2, CN, COOH, COO-C_1-C_4-alkyl, or two R^{14} radicals may represent a bridge $OC(R^{15})_2O$, and

R^{15} is hydrogen, C_1-C_6-alkyl, branched and unbranched, and

R^{16} can be a phenyl, pyridyl, pyrimidyl, pyridazyl, pyrazinyl, pyrazyl, pyrrolyl, naphthyl, quinolyl, imidazolyl ring, which may also carry one or two substituents R^6, and

A is $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_o-$, $-(CH_2)_o-S-(CH_2)_m-$, $-(CH_2)_o-SO-(CH_2)_m-$, $-(CH_2)_o-SO_2-(CH_2)_m-$, $-CH=CH-$, $-C\equiv C-$, $-CO-CH=CH-$, $-(CH_2)_o-CO-(CH_2)_m-$, $-(CH_2)_m-NHCO-(CH_2)_o-$, $-(CH_2)_m-CONH-(CH_2)_o-$, $-(CH_2)_m-NHSO_2-(CH_2)_o-$, $-NH-CO-CH=CH-$, $-(CH_2)_m-SO_2NH-(CH_2)_o-$, $-CH=CH-CONH-$ and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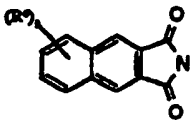
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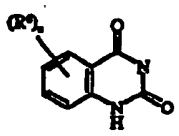
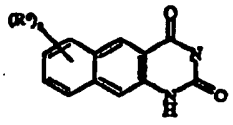

and

[sic]

R^1-A together are also [lacuna] and

B is phenyl, pyridine, pyrimidine, pyrazine, imidazole and thiazole, and

x is 1, 2 or 3, and

n is a number 0, 1 or 2, and

m, o is, independently of one another, a number 0, 1, 2, 3 or 4.

2. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where

B is pyridine or phenyl, and

R^5 is hydrogen, and

R^9 hydrogen, C_1-C_6-alkyl, branched or unbranched, which [lacuna] also carry a substituent R^{16},

R^{16} phenyl which may also carry one or two substituents R^{14}, and

n 0 and 1, and

x 1.

3. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where

B is pyridine or phenyl, and

R^5 is $CONR^{12}R^{13}$, and

R^9 hydrogen, C_1-C_6-alkyl, branched or unbranched, which [lacuna] also carry a substituent R^{16},

R^{16} phenyl which may also carry one or two substituents R^{14}, and

n 0 and 1, and

x 1.

4. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where
B is pyridine or phenyl, and

R^2 is hydrogen

R^5 is hydrogen, and

R^9 hydrogen, C_1-C_6-alkyl, branched or unbranched, which [lacuna] also carry a substituent R^{16},

R^{16} phenyl which may also carry one or two substituents R^{14}, and

n 0 and 1, and

x 1.

5. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where

B is pyridine or phenyl, and

R^2 is hydrogen

R^5 is $CONR^{12}R^{13}$, and

R^9 hydrogen, C_1-C_6-alkyl, branched or unbranched, which [lacuna] also carry a substituent R^{16},

R^{16} phenyl which may also carry one or two substituents R^{14}, and

n 0 and 1, and

x 1.

6. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where

A is $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_o-$, $-(CH_2)_o-S-(CH_2)_m-$, $-CH=CH-$, $-C\equiv C-$,

$-(CH_2)_m-CONH-(CH_2)_o-$,
$-(CH_2)_m-SO_2NH-(CH_2)_o-$, and

B is pyridine or phenyl, and

R^2 is hydrogen, and

R^5 is hydrogen, and

R^9 hydrogen, C_1-C_6-alkyl, branched or unbranched, which may also carry a substituent R^{16}, and

R^{16} phenyl, and

m, n, o 0 and 1, and

x 1.

7. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where

A is $-(CH_2)_m-$, $-(CH_2)_m-O-(CH_2)_o-$, $-(CH_2)_o-S-(CH_2)_m-$, $-CH=CH-$, $-C\equiv C-$, $-(CH_2)_m-CONH-(CH_2)_o-$, $-(CH_2)_m-SO_2NH-(CH_2)_o-$, and

B is pyridine or phenyl, and

R^2 is hydrogen

R^5 is $CONR^{12}R^{13}$, and

R^9 hydrogen, C_1-C_6-alkyl, branched or unbranched, which may also carry a substituent R^{16}, and

R^{16} phenyl, and

m, n, o 0 and 1, and

x 1.

8. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where

B is pyridine or phenyl, and

R^1, R^2 are hydrogen, and

R^5 is hydrogen, and

R^9 hydrogen, C_1-C_6-alkyl, branched or unbranched, which may also carry a substituent R^{16}, and

R^{16} phenyl, and

m, n, o 0, and

x 1.

9. An amide with heterocyclic substituents, of the formula I, as claimed in claim 1, where

B is pyridine or phenyl, and

R^1, R^2 are hydrogen

R^5 is $CONR^{12}R^{13}$, and

R^9 hydrogen, C_1-C_6-alkyl, branched or unbranched, which may also carry a substituent R^{16}, and

R^{16} phenyl, and

m, n, o 0

x 1.

10. The use of amides of the formula I as claimed in claims 1-5 for treating diseases.

11. The use of amides of the formula I as claimed in claims 1-5 as inhibitors of cysteine proteases.

12. The use as claimed in claim 6 as inhibitors of cysteine proteases such as calpains and cathepsins, in particular calpains I and II and cathepsins B and L.

13. The use of amides of the formula I as claimed in claims 1-5 for production as pharmaceuticals for treating diseases in which elevated calpain activities occur.

14. The use of amides of the formula I as claimed in claims 1-5 for producing pharmaceuticals for treating neurodegenerative disorders and neuronal damage.

15. The use as claimed in claim 9 for treating neurodegenerative disorders and neuronal damage induced by ischemia, trauma or massive bleeding.

16. The use as claimed in claim 10 for treating stroke and craniocerebral trauma.

17. The use as claimed in claim 10 for treating Alzheimer's disease and Huntington's disease.

18. The use as claimed in claim 10 for treating epilepsies.

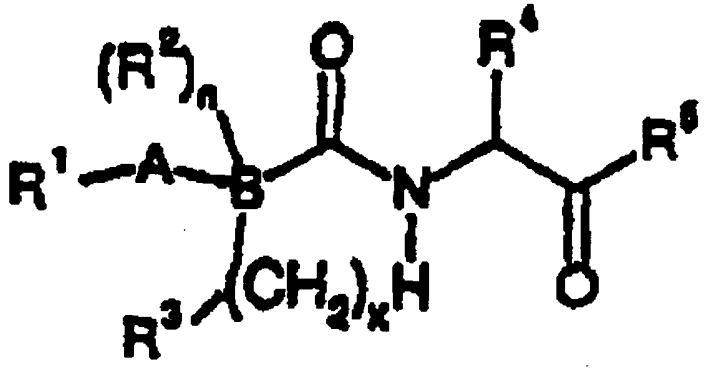
19. The use of compounds of the formula I as claimed in claims 1-5 for producing pharmaceuticals and [sic] treating damage to the heart after cardiac ischemias, damage to the kidneys after renal ischemias, skeletal muscle damage, muscular dystrophies, damage produced by proliferation of smooth muscle cells, coronary vasospasm, cerebral vasospasm, cataracts of the eyes and restenosis of blood vessels after angioplasty.

20. The use of amides of the formula I as claimed in claims 1-5 for producing pharmaceuticals for treating tumors and metastasis thereof.

21. The use of amides of the formula I as claimed in claims 1-5 for producing pharmaceuticals for treating disorders in which elevated interleukin-1 levels occur.

22. The use of amides according to claims 1-5 for treating immunological disorders such as inflammations and rheumatic disorders.

23. A pharmaceutical preparation for oral, parenteral or intraperitoneal use, comprising at least one amide I as claimed in claims 1-5 per single dose, besides conventional pharmaceutical ancillary substances.



(I)